Spring 2016

I. Zinc mediated homologation-cyclopropanation in beta diketones and selectivity within cyclopropanoxide rearrangements. II. Zinc mediated tandem chain extension-aldol reaction and formation of substituted gamma lactones

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I. ZINC-MEDIATED HOMOLOGATION-CYCLOPROPANATION IN β-DIKETONES AND SELECTIVITY WITHIN CYCLOPROPANOXIDE REARRANGEMENTS.

II. ZINC-MEDIATED TANDEM CHAIN EXTENSION-ALDOL REACTION AND FORMATION OF SUBSTITUTED γ-LACTONES.

By

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M.S., Montclair State University, 2011

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On January 21, 2016

Original approval signatures are on file with the University of New Hampshire Graduate School.

DEDICATION

This thesis is dedicated to my parents, my Uncle Dr. T.M. Bala and my Research advisor for their immense support and co-operation and most of all God Almighty for the endurance and well being that were necessary to complete this thesis.

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TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

I. ZINC-MEDIATED HOMOLOGATION-CYCLOPROPANATION IN β-DI KETONES AND SELECTIVITY WITHIN CYCLOPROPANOXIDE REARRANGEMENTS.

II. ZINC-MEDIATED TANDEM CHAIN-EXTENSION-ALDOL REACTION AND FORMATION OF SUBSTITUTED γ-LACTONES.

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Kaushik Bala

University of New Hampshire, May 2016

The investigation of homologation-cyclopropanation in β-diketones revealed the involvement of two donor-acceptor cyclopropane intermediates. Cyclopropanoxide rearrangements were accomplished using reaction conditions other than zinc-carbenoid. Ring fragmentation within chain-extended tertiary cyclopropanoxides was investigated under acidic and basic reaction conditions.

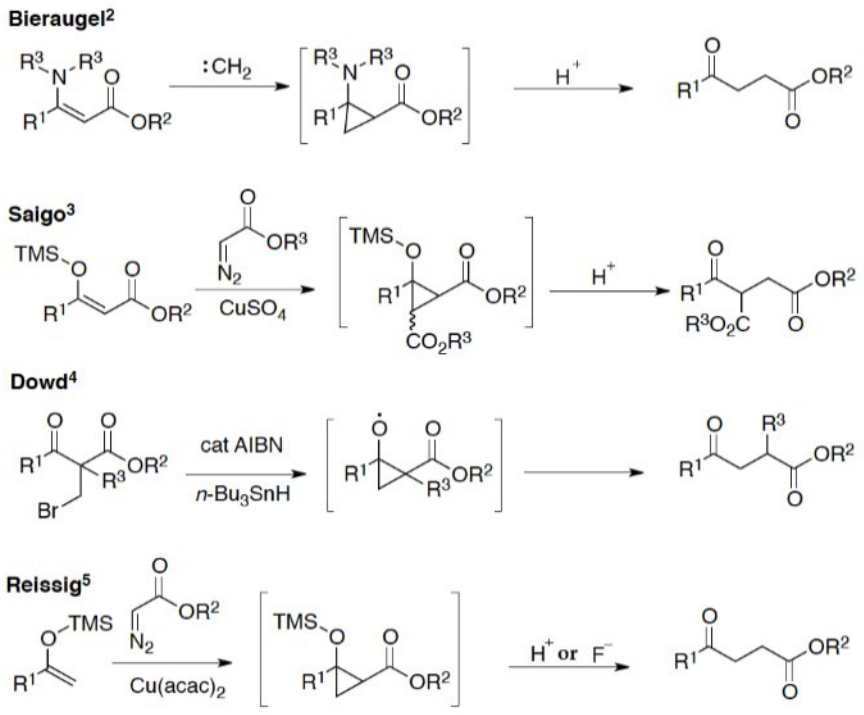
Tandem chain extension-aldol reaction and lactonization were accomplished using α-carboxyester imides. A diastereomeric mixture of substituted γ-lactones (*cis* and *trans*) was isolated and characterized by NMR studies. Increased diastereomeric ratios of the *trans* substituted γ-lactones versus their *cis* counterparts were attributed towards increased *syn*-aldol selectivity due to chelation of the zinc-bound ester enolate with the imide carbonyl of the chiral auxiliary.

Chapter 1

Introduction

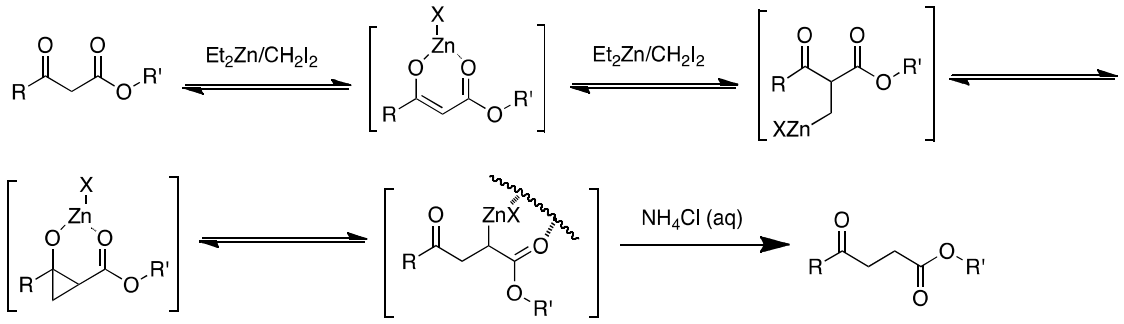
1.1 Background of chain homologation-cyclopropanation:

1,4-Diketones have been demonstrated to be useful substrates for the synthesis of cyclic enones.[1] One carbon-homologation involving the insertion of a single methylene (i.e. CH_2) unit has been used as an effective synthetic tool for the efficient conversion of β-diketones (i.e. 1,3-diketones) to γ-diketones (i.e. 1,4-diketones). This method was developed over the years by Bieraugel,[2] Saigo,[3] Dowd[4] and Reissig[5] involving the intermediacy of a donor-acceptor (push-pull) cyclopropane[6] (**Scheme 1.0**).



Scheme 1.0: Chain extension reactions through donor-acceptor cyclopropanes

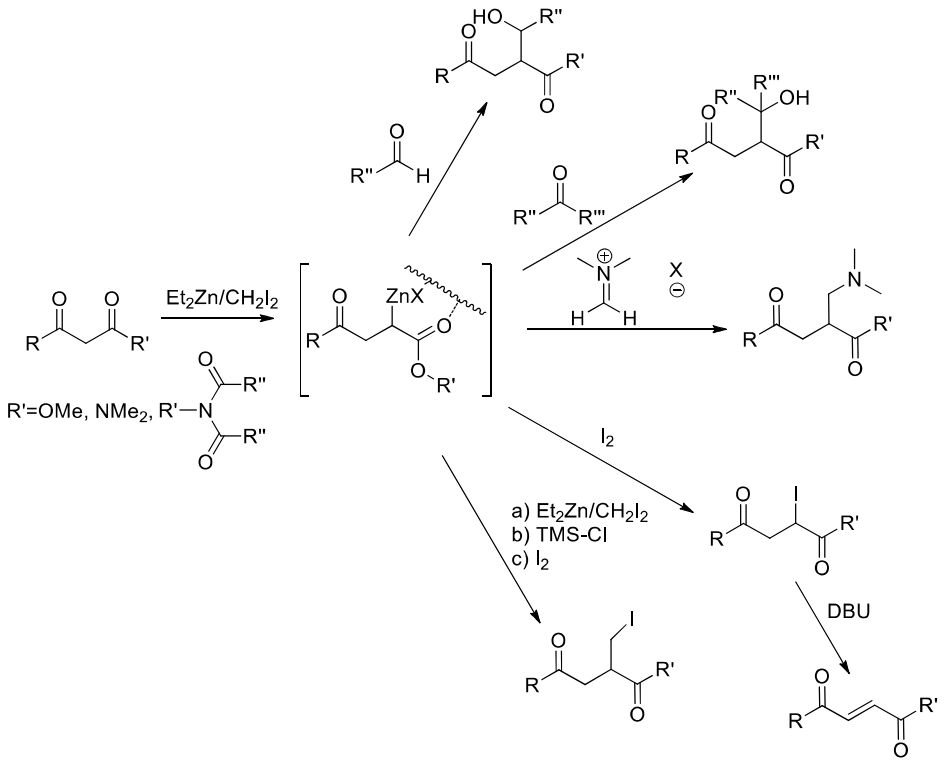
Brogan and Zercher contributed to the area of chain homologation by describing the development of an efficient one-pot synthesis of γ-keto esters from β-keto esters[7] (**Scheme 1.1**). This process was accomplished by using the Furukuwa carbenoid [i.e. ethyl(iodomethyl)zinc], which is a variant of the Simmons-Smith reagent [i.e. Copper activated iodomethylzinc iodide].[8a-d]



Scheme 1.1: Proposed homologation mechanism of a β-keto ester[7]

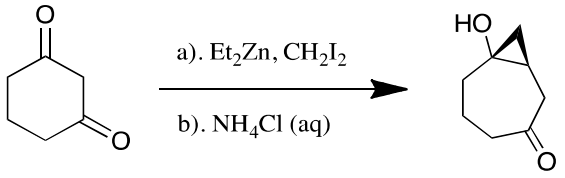
Tandem homologation-cyclopropanation reactions with β-keto substrates were exploited to trap a variety of electrophiles such as aldehydes and ketones,[9] iminium ions,[10] halogens[11] and excess carbenoid[12] to introduce substituents at the α-position (such as hydroxymethyl, methyl and iodomethyl).[17] The β-position could also be modified with alkyl or aryl substituents through the use of modified carbenoids (**Scheme 1.2**).

Additional investigations by Zercher group members have expanded the domain of the β-keto substrates to include β-keto amides, [12] β-keto phosphonates,[13] β-keto imides, [14] α-carboxyester imide,[15] and diimides.[16] The construction of complex ring systems[18,19] have also been accomplished.



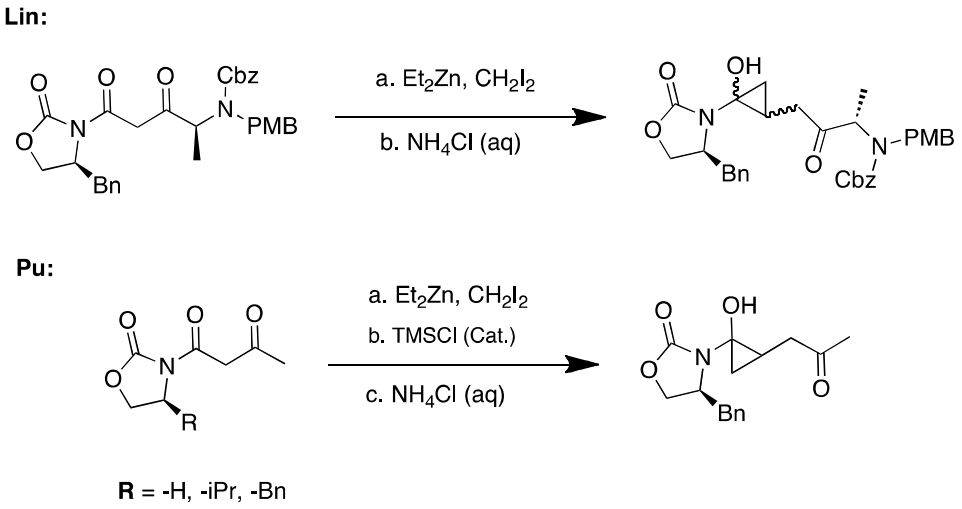
Scheme 1.2: Tandem chain homologation processes

Brogan and Zercher observed the formation of cyclopropanol byproducts upon exposure of a cyclic β-diketone to excess carbenoid (**Scheme 1.3**). This unexpected cyclopropanol by-product was believed to be formed by ring homologation followed by a second methylene insertion.[6]



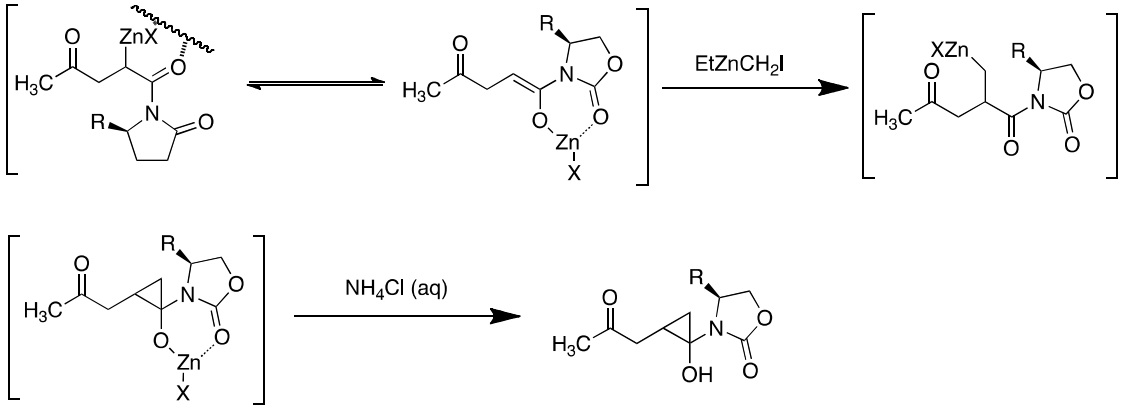
Scheme 1.3 – Homologation-cyclopropanation of a cyclic β-diketone

Previous Zercher group members also observed the formation of cyclopropanol byproducts during tandem homologation reactions of β-keto imides (**Scheme 1.4**).[14,17]



Scheme 1.4: Initially unexpected cyclopropanol byproducts

These results obtained for β-diketones and β-keto imides were very different than those observed for a typical β-keto ester. This was attributed to the decreased stability and increased nucleophilicity of the Reformatsky organometallic intermediate formed within β-diketones and β-keto imides (**Scheme 1.5**).



Scheme 1.5: Formation of more reactive Reformatsky organometallic intermediate in β-keto imides

A Reformatsky organometallic intermediate generated within β-keto imides and β-diketones has the potential for isomerization to the more reactive zinc enolate resulting in further alkylation in

the presence of excess Furukawa carbenoid under the reaction conditions.[14,17,21] Hilgenkamp reported that use of chlorotrimethylsilane (TMSCl) under the reaction conditions promotes the formation of a α-methylated homoenolate intermediate within β-keto esters and β-keto amides due to disruption of the stable Reformatsky-like intermediate.[12] Such alkylations, however, did not occur within β-keto esters, presumably due to the oligomeric nature of its Reformatsky organometallic intermediate (i.e. carbon bound zinc enolate) which is less nucleophilic than a typical enolate (**Figure 1**).[20,21]

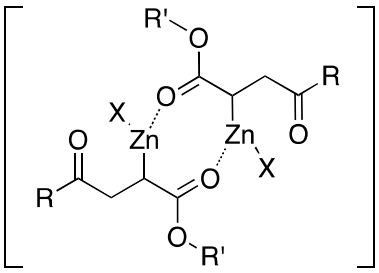


Figure 1: Proposed oligomeric nature of a Reformatsky-like organometallic intermediate

1.2 Inhibition of HIV Aspartyl Protease using Peptidomimetics:

Peptidomimetics has proven to be a uselful synthetic tool for the inhibition of the enzyme HIV aspartyl protease. The main function of the enzyme is the site-specific hydrolytic cleavage of the polypeptide chain to produce peptide fragments necessary for viral replication.[18]

Scheme 1.6: Aspartyl protease promoted peptide hydrolysis

Successful inhibition of the enzyme aspartyl protease has involved the isosteric replacement of the amide linkage with functionalities resistant to enzymatic hydrolysis such as a ketomethylene unit or with functional modifications mimicking the tetrahedral intermediate e.g. hydroxyethylene unit (**Figure 2**).

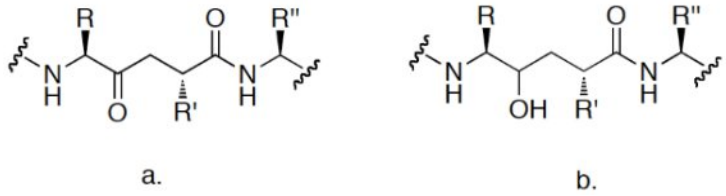


Figure 2: Potential isosteric replacements: a. Ketomethylene and b. Hydroxyethylene

Inhibitors for HIV aspartyl protease were selectively designed to be competitive and fast binding with the target enzyme.[23,24,25] Cyclopropyl-containing peptide isosteres were considered another alternative for designing more rigid isosteric replacements to the amide bond. Conformational rigidity and restricted rotation around the carbon-carbon bond imparted by the cyclopropyl residue were suggested as features to enhance enzyme binding and provide hydrolytic stability. Wipf and co-workers designed rigid tri-substituted alkenyl dipeptide isosteres, which were then converted to analogous cyclopropyl isosteres by Martin and co-workers (**Figure 3**).[24,25]

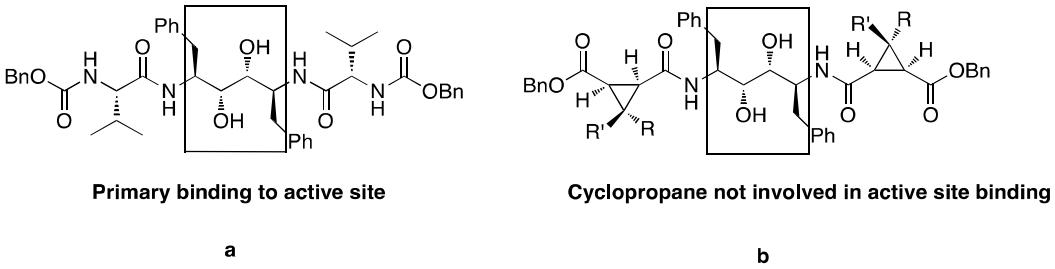


Figure 3: Known HIV-1 inhibitor (a) and modified cyclopropyl isosteres (b)

Loss of hydrogen bonding capability of a cyclopropane ring within the active site of the target enzyme would compromise its synthetic utility.

Zercher group members believed that inclusion of cyclopropanols within these peptide isosteres by zinc-mediated homolgation-cyclopropanation reaction could exhibit excellent inhibition efficiency of the target enzyme due to being non-hydrolyzable, conformationally biased due to restricted rotation and capable of hydrogen bonding (**Figure 4**).

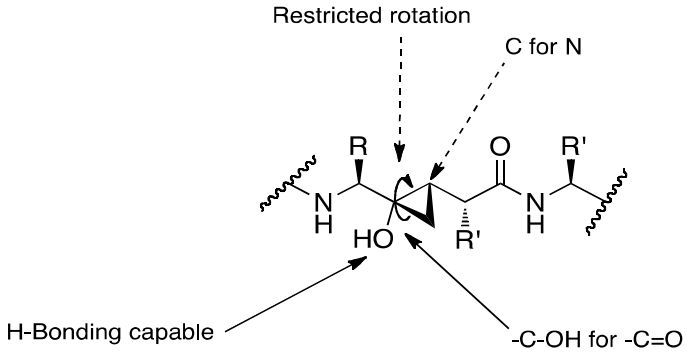


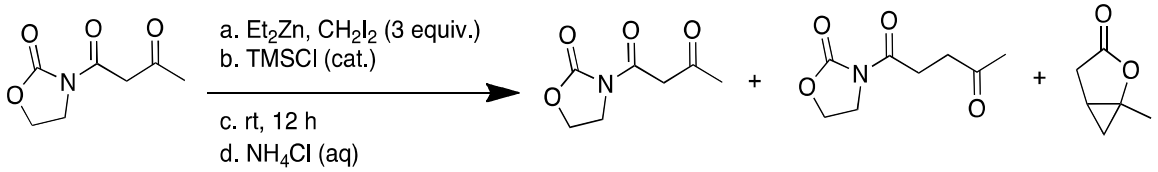
Figure 4: Unique cyclopropanol peptide-isostere

The unique structure of these cyclopropanol byproducts were conceptualized as synthetic building blocks in the field of medicinal chemistry, since individual carbons within this cyclopropanol peptide isostere are capable of being modified stereoselectively. This offers a unique advantage to design reactions wherein use of amino acids as starting materials provides the environment for inclusion of cyclopropanols as part of the peptide isostere.

1.3 Methodology of homologation-cyclopropanation:

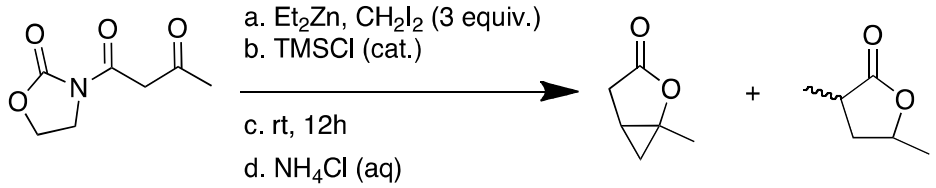
Following the seminal work of Lin and Pu, Ian Taschner a previous Zercher group member investigated the methodology of chain-homologation in an attempt to obtain the cyclopropanol byproduct. However the reaction resulted in the identification of a bicyclic lactone (**Scheme 1.7**) rather than the predicted cyclopropanol as observed by Lin and Pu. The formation of the chain

homologated γ-keto imide and the unreacted starting material (i.e. β-keto imide) within the reaction mixture was attributed to the quenching of the Furukuwa carbenoid due to its reaction with trace amounts of HCl being present within chlorotrimethylsilane (TMSCl).[21,22,26]



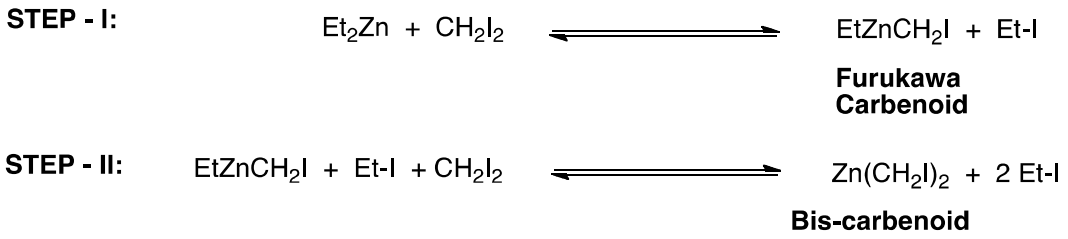
Scheme 1.7: Initial attempts of homologation-cyclopropanation of a β-keto imide

Attempts to reproduce the experimental methodology using five equivalents of the Furukuwa carbenoid resulted in the formation of the bicyclic lactone (Taschtone) along with the α-methyl-γ-valerolactone (**Scheme 1.8**). Taschner believed that the latter byproduct was obtained as a result of an intramolecular Meerwin-Ponndorf-Verley like reduction.[27]



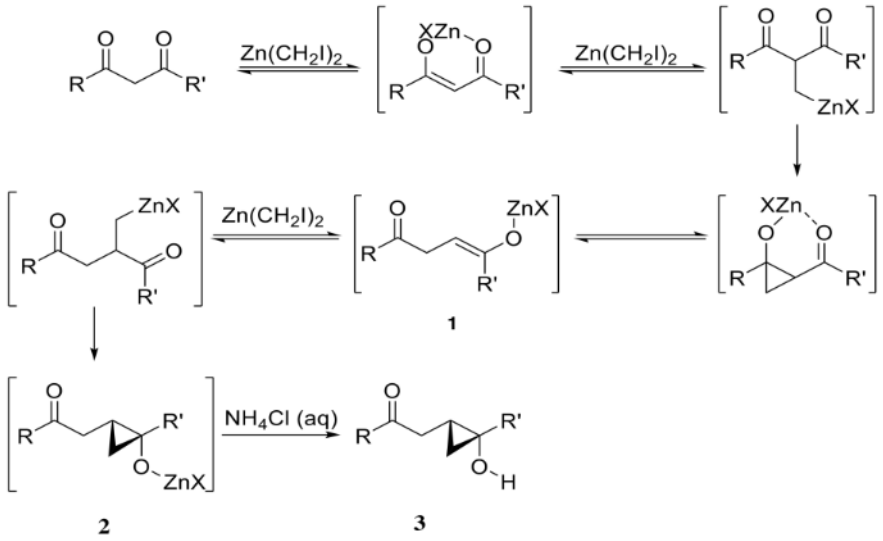
Scheme 1.8: Formation of the bicylic lactone and α-methyl- γ-valerolactone

To circumvent the possibility of a Meerwin-Ponndorf-Verley like reduction, Zercher group members proposed the utilization of bis(iodomethyl)zinc [i.e. $Zn(CH_2I)_2$] also called the "*bis-carbenoid*".[28] This carbenoid variant has an electronic structure similar to the Furukawa-modified carbenoid and involves the use of 5 equivalents of diethylzinc and 10 equivalents of diiodomethane (**Scheme 1.9**).[8,28,29]



Scheme 1.9: Proposed reaction scheme for the formation of bis(iodomethyl)zinc

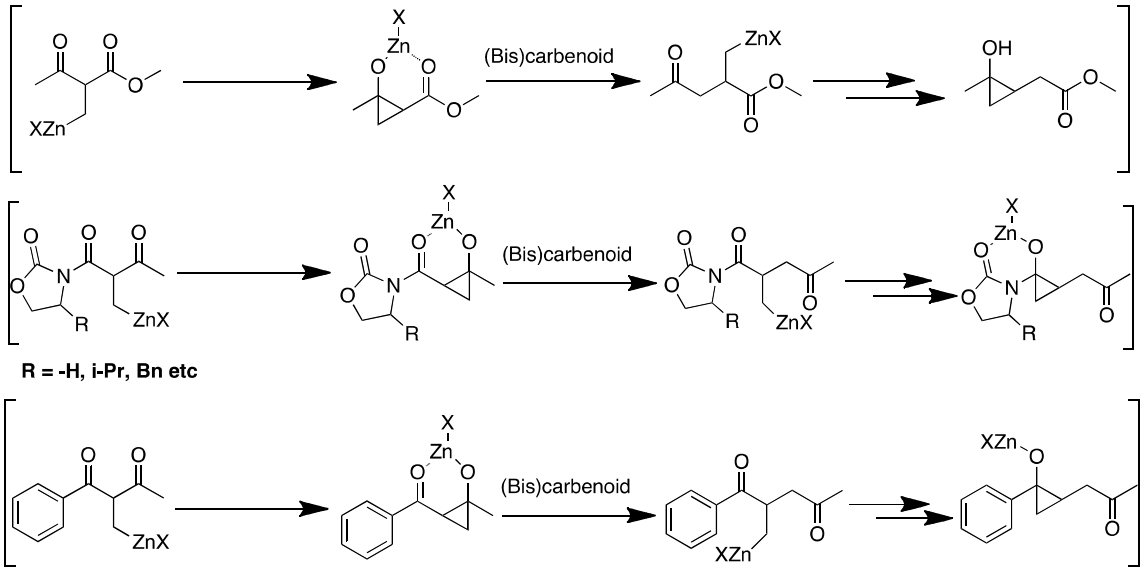
The proposed mechanism for the homologation-cyclopropanation reaction within the Zercher group (**Scheme 2.0**) involves the use of two equivalents of the carbenoid species [i.e. bis(iodomethyl)zinc – $Zn(CH_2I)_2$]. The intermediate is believed to be a donor-acceptor cyclopropane,[30] which undergoes fragmentation resulting in the formation of the latent enolate **1**. This latent enolate, however, reacts with a third equivalent of the carbenoid species resulting in the formation of a second homoenolate, which in turn undergoes a second intramolecular nucleophilic attack to generate the alkyl substituted γ-keto cyclopropoxide **2**. The γ-keto cyclopropanol **3** is formed upon a mild acidic quench (**Scheme 1.10**).



Scheme 1.10 – Proposed mechanism for the homologation-cyclopropanation of a β-dicarbonyl substrate

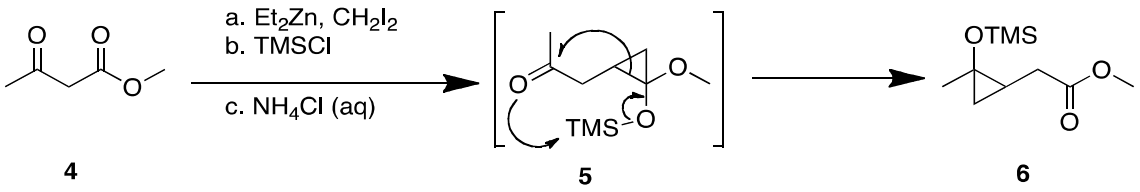
1.4 Regioselective formation of Cyclopropanols:

Regioselective cyclopropanations were observed primarily due to variation in substituents (R or R') attached to either ends of the dicarbonyl substrate. However, the mechanistic pathway was proposed to involve the cyclization of the initially formed nucleophilic zinc species (i.e. homoenolate) into the most electrophilic carbonyl carbon of the β-dicarbonyl substrate to form a donor-acceptor cyclopropane intermediate. This, in turn, fragments to form the chain extended cyclopropanoxide under reaction conditions (**Scheme 1.11**).



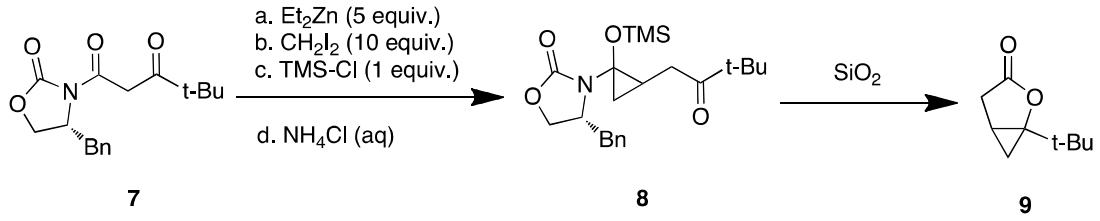
Scheme 1.11: Mechanistic pathways for the formation of chain extended regioisomeric cyclopropanoxides

Initial attempts to observe homologation-cyclopropanation within a β-keto ester **4** was first explored by Taschner.[26] He observed that the cyclization of the initially formed zinc homoenolate occurs into the carbonyl of the methyl ketone rather than the ester carbonyl. The regiochemistry of the rearranged cyclopropyl TMS ether **6** was proposed to occur by a sigmatropic rearrangement of **5** under the reaction conditions (**Scheme 1.12**).



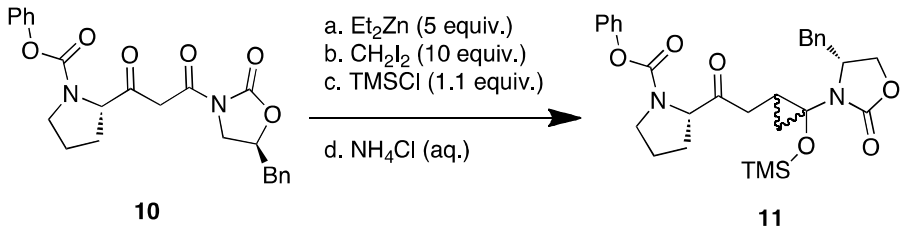
Scheme 1.12: TMSCl mediated homologation-cyclopropanation in β-keto esters

Similar observations reported earlier for homologation-cyclopropanation studies conducted using β-keto imides depicted that donor-acceptor cyclopropane formation takes place with the carbonyl of the methyl ketone as opposed to the imide carbonyl.[14,17,26] In **Scheme 1.13**, the regioisomeric cyclopropanoxide resulting from **7** was intentionally trapped as its cyclopropyl TMS ether **8** due to its potential to rearrange further into the regioisomeric t-butyl cyclopropanoxide (structure not shown) followed by subsequent formation of the bicyclic lactone **9**. It is worth noticing that the regioisomeric t-butyl cyclopropanol or its trimethylsilyl (TMS) ether were never isolated under the reaction conditions. This could possibly be rationalized due to a rapid transformation of the regioisomeric t-butyl cyclopropanoxide to the bicyclic lactone with the expulsion of chiral oxazolidinone.[26]



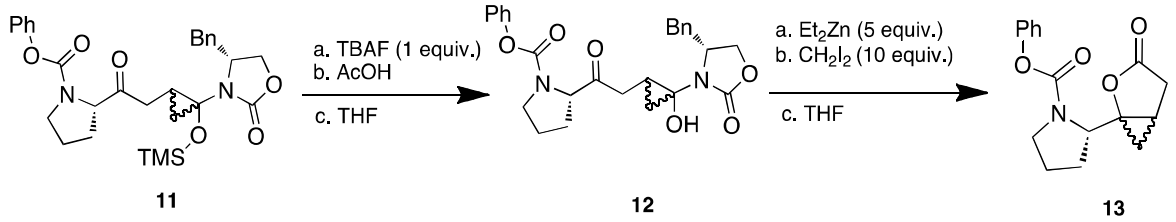
Scheme 1.13: Formation and deprotection of the putative TMS-cyclopropyl ether

Based on the observations reported by Taschner, Zercher group members[34,35] also explored that use of proline derived β-keto imide **10**, which resulted in the formation of a mixture of diastereomeric TMS protected cyclopropyl ethers **11** under homologation-cyclopropanation conditions (**Scheme 1.14**).



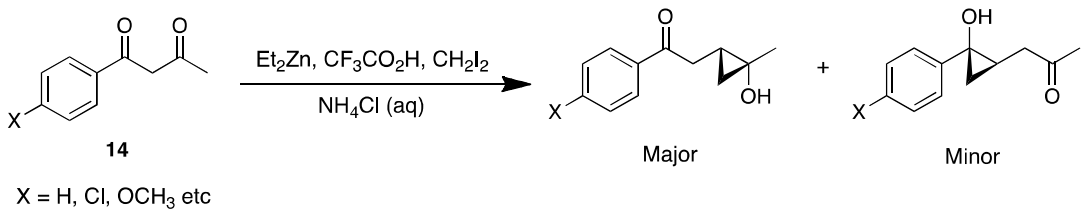
Scheme 1.14: Homologation-cyclopropanation of proline derived β-keto imides

A combination of tetra-n-butylammonium fluoride (TBAF) and acetic acid was used to deprotect the cyclopropyl ethers **11** and form their corresponding alcohols **12**.[34] Subjecting this diastereomeric mixture of regioisomeric cyclopropanols to homologation-cyclopropanation conditions resulted in the formation of diastereomeric lactones **13** thereby indicating the involvement of cyclopropanoxide rearrangements in the formation of the bicyclic lactone **13** (**Scheme 1.15**).[34,35]



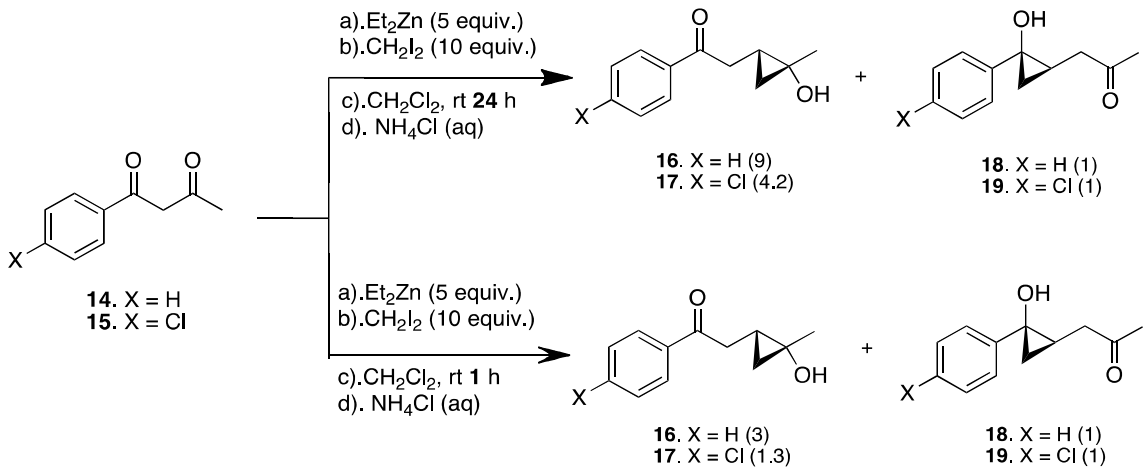
Scheme 1.15: Proposed cyclopropanoxide rearrangement followed by lactonization

Results obtained by Xue and co-workers[31] for homologation-cyclopropanation of the β-diketone **14** suggested that formation of the major cyclopropanol could have arisen due to the formation of the initial donor-acceptor cyclopropane intermediate at the aryl ketone (**Scheme 1.16**).



Scheme 1.16: Unexpected distribution of regioisomeric cyclopropanols

However this regioselective product distribution was not consistent with the model used by the Zercher group in predicting the formation of the initial donor-acceptor cyclopropane intermediate. Mower and Zercher proposed a time-dependent study of the cyclopropanoxide formation. Mower[32] determined experimentally that the "major" product formed under extended reaction times (*Thermodynamic control*) was the methyl cyclopropanol (**16** and **17)** while a nearly 1 : 1 mixture of regioisomeric cyclopropanols were formed under reduced reaction times (**Scheme 1.17**).

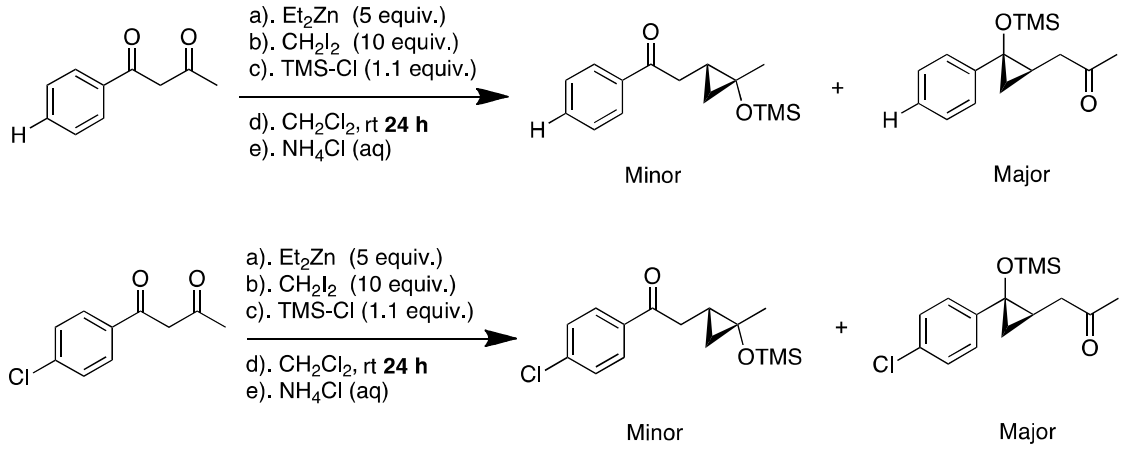


Scheme 1.17: Time-dependent distribution of regioisomeric cyclopropanols

The formation of these regioisomeric cyclopropanols (**16** and **18**) in a 1 : 1 ratio was suggestive of the fact that the donor-acceptor cyclopropane intermediate was forming with the methyl ketone as opposed to the conjugated aryl ketone. This formed the basis of a hypothesis within the

Zercher group which postulated that, "*it were these regioisomeric cyclopropanols (**16** and **18**) forming initially under the reaction conditions and rearranging over the course of the reaction to yield the thermodynamic mixture with **16** being the major product*".

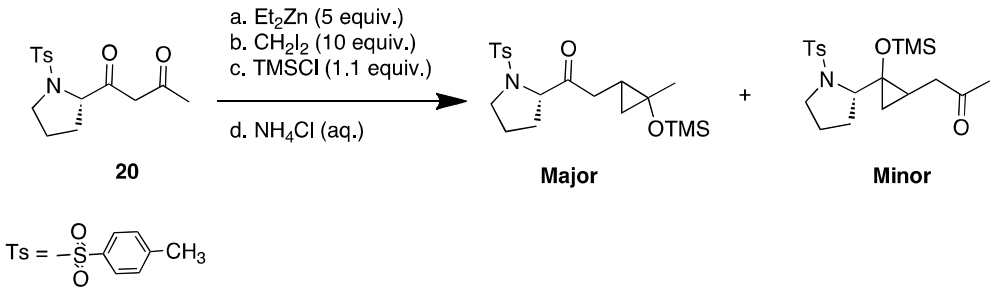
Trapping these regioisomeric cyclopropanoxides as their trimethylsilyl (TMS) ether derivatives using chlorotrimethylsilane (TMS-Cl) supported this hypothesis. The ratios of the TMS-protected cyclopropanols in the crude reaction mixture were determined from the final ratio of the cyclpropanols formed by deprotection of the trimethylsilyl group **(Scheme 1.18**).[32]



Ratios of the TMS-protected cyclopropanols within the crude reaction mixture were determined using final ratio of deprotected cyclopropanols (Scheme 1.17**).*

Scheme 1.18: Trapping regioisomeric cyclopropanols using TMSCl

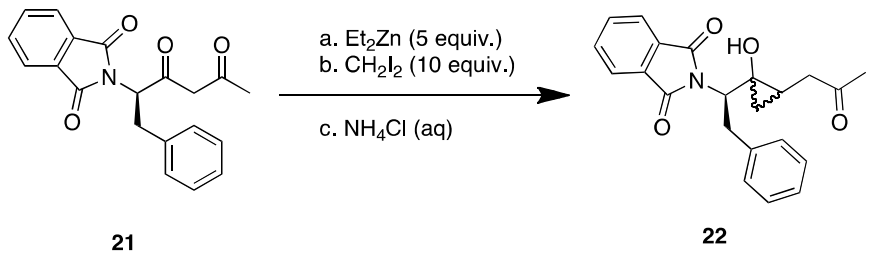
Methyl and proline-substituted asymmetric diketone system **20** was also selected by Mower[32] to probe the reaction in the presence of chlorotrimethylsilane (TMSCl) (**Scheme 1.19**). The *major* regioisomeric cyclopropanol appeared to be a result of the initial homoenolate cyclizing into the ketone adjacent to the proline system (i.e. ketone located β to the sulfonamide moiety) as opposed to the methyl ketone.



Scheme 1.19: Homologation-cyclopropanation of proline-and methyl-substituted β-diketone

The regioselectivity in this case was attributed to the electron withdrawing nature of the sulfonamide moiety that increases the electrophilicity of the carbonyl adjacent to the proline system. Stereochemical investigations of their configuration using Nuclear Overhauser Enhancement (NOESY) studies confirmed the stereochemistry of these cyclopropanol moieties, which possessed the hydroxyl (-OH) group and the ketone bearing alkyl chain (R) "***cis***" to one another. These results were consistent with the structures reported by Xue and co-workers.

Current studies on regioselective cyclopropanations within the Zercher group involve subjecting phthalimide-protected β-diketones[14] to homologation-cyclopropanation conditions. It was observed that exposing a pthalamide-protected β-diketone **21** to bis-carbenoid results in the formation of a diastereomeric mixture of chain extended cyclopropanols **22** (**Scheme 3.0**).[33] This was explained by formation of the donor-acceptor cyclopropane with the ketone adjacent to the phthalimide and the benzyl group, followed by fragmentation and cyclopropanation to form the intermediate chain extended methyl cyclopropanoxide (product not shown). This chain extended methyl cyclopropanoxide is proposed to undergo a cyclopropanoxide rearrangement resulting in the formation of **22** once again supporting that the electron-withdrawing nature of the phthalimide functionality and its potential for chelation with the adjacent ketone increases its electrophilicity thereby explaining the regioselectivity in product formation.



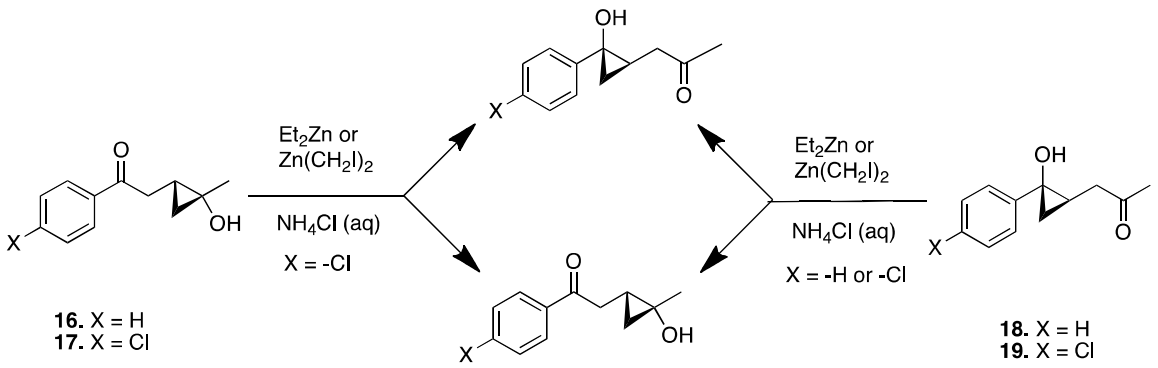
21 22

Scheme 1.20: Proposed homologation-cyclopropanation of Pthalamide-protected β-diketones

1.5 Cyclopropanoxide rearrangements:

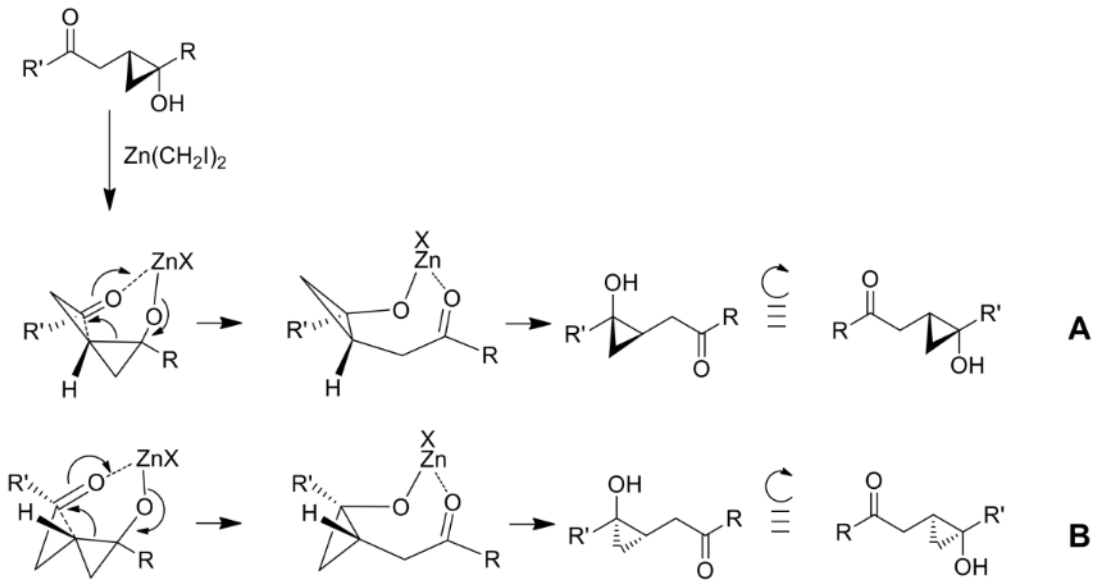
The results obtained earlier (**Scheme 2.7**) led Mower and Zercher to propose that reduced reaction times would result in the formation of cyclopropanol regioisomers, **18** and **19** and that these regioisomers (**18** and **19)** (*kinetic control*) forming under reduced reaction times were rearranging to **16** and **17 (***Thermodynamic Control*) under extended reaction times. The general nature and the scope of these cyclopropanoxide rearrangements were confirmed by isolating the individual cyclopropanol regioisomers **18** and **19** and re-exposing them to the bis-carbenoid [$Zn(CH_2I)_2$]. The reaction resulted in a direct interconversion of a single cyclopropanol regioisomer to a mixture of two regioisomers in a 1 : 1 ratio, which provided direct evidence of the cyclopropanoxide rearrangement. Similar results were obtained using diethylzinc (Et_2Zn), which indicated that the interconversions of the cyclopropanol regioisomers **18** and **19** occur through a zinc alkoxide species and that the zinc-carbenoid species is not a necessary component of the rearrangement mechanism (**Scheme 1.21**).

Similarly rearrangement of the methyl cyclopropanoxide **17** to a mixture of **17** and **19** was also observed on exposing the methyl cyclopropanol **17** to bis-carbenoid [$Zn(CH_2I)_2$]. However no attempt was made to observe the methyl cyclopropanoxide **16** interconvert to a mixture of **16** and **18** using the bis-carbenoid [$Zn(CH_2I)_2$].



Scheme 1.21: Interconversion of cyclopropanol regioisomers

The proposed mechanism for this rearrangement involves the chelation of a zinc species between the cyclopropanoxide and the carbonyl moieties resulting in a seven membered ring transition state (**Scheme 1.22**).



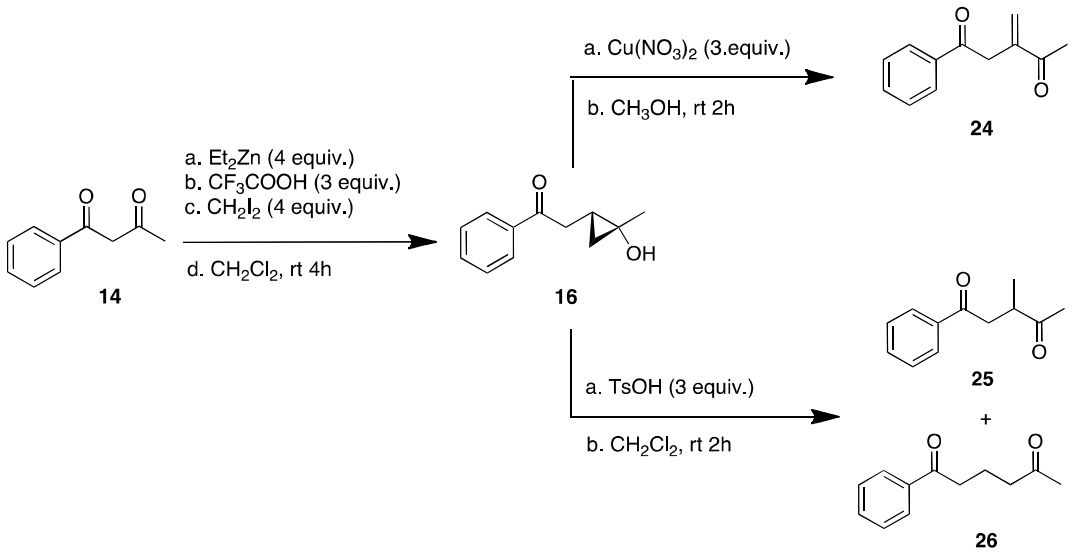
Scheme 1.22: Proposed cyclopropanol rearrangement mechanism

Computational studies of acyclic β-diketones resulted in the identification of two stereochemically distinct geometries (**A** and **B**) in the cyclopropanoxide rearrangement.[34]

1.6 Ring Fragmentation of Tertiary Cyclopropanols:

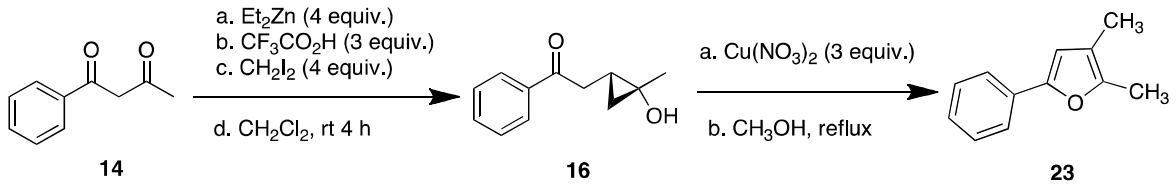
The chain extended tertiary cyclopropanols obtained from β-diketones are known to undergo ring fragmentation reactions under both acidic and basic reaction conditions.[36] This unique reactivity is due to angle and eclipsing strain present within the cyclopropane ring of the tertiary cyclopropanols with angle strain being especially severe.[37] Li and co-workers have reported the ring opening reactions of *trans*-1,2–di-substituted cyclopropanol **16** prepared from the β-diketone **14**.[38]

These reactions were mediated by $Cu(NO_3)_2$ and *p*-toluenesulphonic acid (*p*-TsOH) to yield mainly the α-methylene diketone **24** and α-methyl-γ-diketone **25** along with minor amounts of the chain extended δ-diketone **26** (**Scheme 1.23**).



Scheme 1.23: Acid and metal catalyzed ring fragmentation reaction of a tertiary cyclopropanol

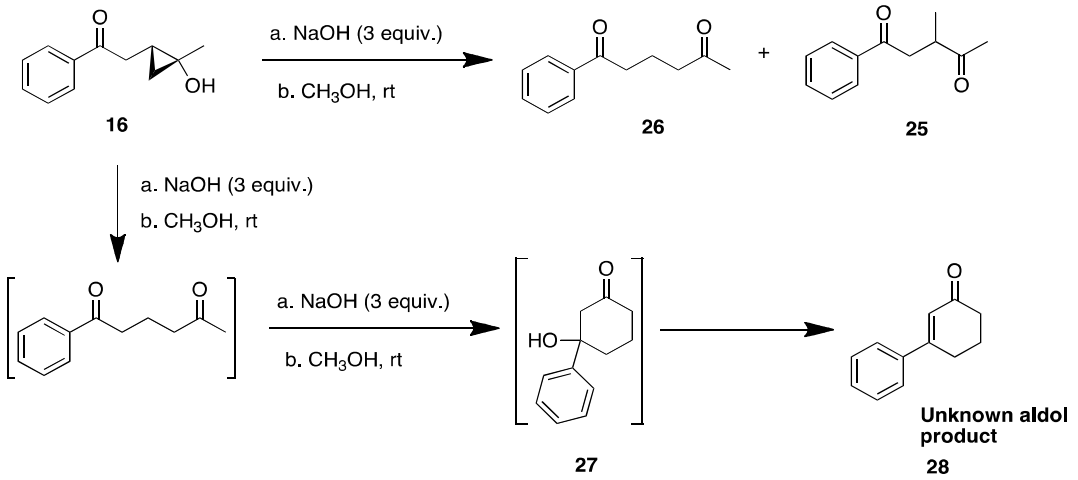
However 2,3,5-substituted furans **23** were obtained in high yields when the ring cleavage in tertiary cyclopropanols was facilitated using *p*-TsOH in methanol under refluxing conditions (**Scheme 1.24**).



Scheme 1.24: Formation of substituted Furans from ring fragmentation of a tertiary cyclopropanol.

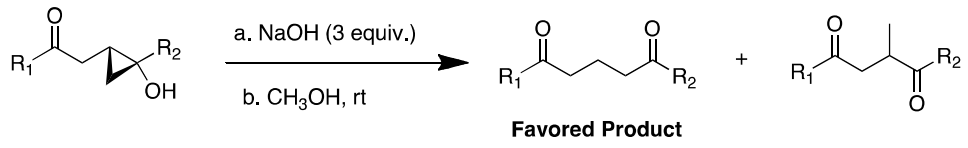
Li and co-workers[38] concluded that acid-catalyzed ring fragmentation reaction of cyclopropanol **16** resulted in the preferential formation of the α-methyl-γ-diketone **25** along with minor amounts of the chain extended δ-di ketone **26** under the reaction conditions described in **Scheme 3.2**. On the contrary, ring fragmentation of the regioisomeric cyclopropanol **16** under base-catalyzed reaction conditions resulted in the formation of a complex mixture comprising the α-methyl-γ-diketone **25**, the chain extended δ-diketone **26** and an unknown product resulting from the aldol condensation of **26**.

Initial research on cyclopropanoxide rearrangements of **16** within the Zercher group led to the belief that the unknown aldol product within the crude mixture could possibly have been the (*enone*) 3-phenyl-2-cyclohexen-1-one **28,** which might have resulted from an intramolecular aldol condensation of **26** to yield the (*ketol*) 3-hydroxy-3-phenylcyclohexanone **27** followed by an elimination reaction under the reaction conditions (**Scheme 1.25**).



Scheme 1.25: Proposed intramolecular aldol condensation and elimination of a δ-di ketone

Li and co-workers[38] have also reported that incorporation of bulky substituents and increased conjugation within β-diketones resulted in the preferential formation of the chain extended δ-diketone as opposed to the α-methyl-γ-diketone under base catalyzed reaction conditions (**Scheme 1.26**). However a mechanistic rationale was not proposed to support this conclusion.

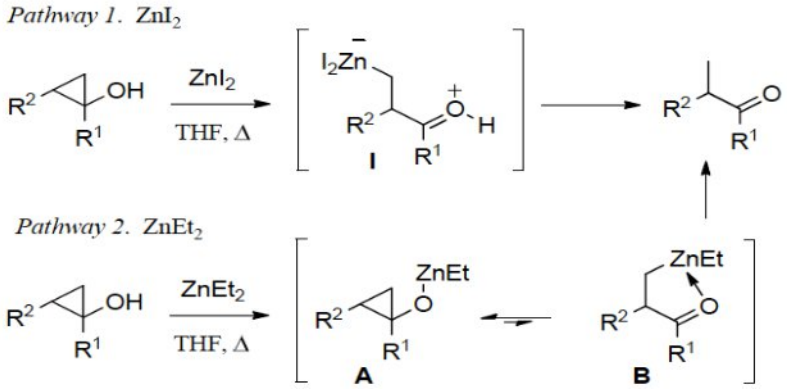


R1 = -Phenyl, -p-Me-O-C_6H_4, -m,p-Me-O-C_6H_4
R2 = -Phenyl, n-C_3H_7, -p-Me-O-C_6H_4

Scheme 1.26: Ring fragmentation of cyclopropanols with bulky substituents

Cha and co-workers[39] recently reported a similar regioselective ring opening of tertiary cyclopropanols using organozinc reagents. Two mechanistic pathways involving the intermediacy of a zinc homoenolate that leads to the formation of the α- or β-alkylated γ-diketones. Cha and co-workers believed that the zinc cyclopropanoxide **A** could be in equilibrium with the homoenolate **B** where the former was expected to be strongly favored.[40,41,48]

Cha and co-workers report that efforts to trap the homoenolate were still under investigation (**Scheme 1.27**).

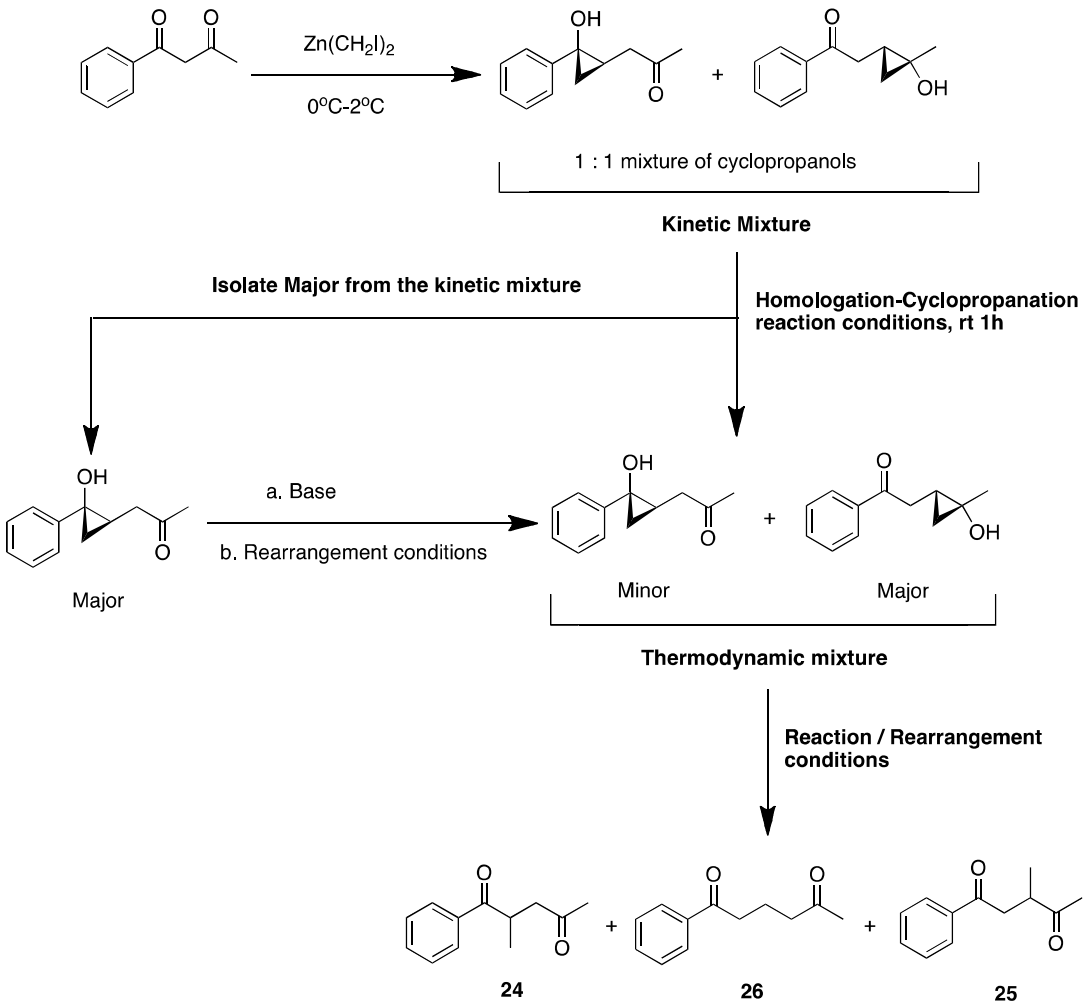


Scheme 1.27: Organozinc-mediated ring opening of tertiary cyclopropanols

Risatti[57] in an attempt to observe the formation of the chain-extended γ-keto cyclopropanols **18** and **16** reported that Furukawa carbenoid-mediated ($EtZnCH_2I$) homologation-cyclopropanation of the β-diketone **14** also resulted in the formation of the α-methylated γ-diketone **25** and the chain-extended δ-diketone **26**. Initial results reported by Risatti[57] and Mower[32] led Zercher group members to propose that formation of the ring fragmented by-products **25** and **26** were resulting from the ring fragmentation of the methyl cyclopropanoxide **16** and that **16** was obtained from the aryl cyclopropanoxide **18** due to a cyclopropanoxide rearrangement.

The proposed reaction plan as a part of this study was to isolate increased amounts of aryl cyclopropanol **18** from the *kinetic mixture* (i.e. 1 : 1 mixture of the regioisomeric cyclopropanoxides **18** and **16**) and then subjecting it to base-mediated rearrangement conditions [Et_2Zn or $Zn(CH_2I)_2$] to yield the *thermodynamic mixture* containing the methyl cyclopropanoxide **16** (*major component*)**.** The methyl cyclopropanoxide **16** is possibly believed

to undergo ring cleavage under the reaction conditions resulting in the formation of α-methyl-γ-diketone **25** along with the chain extended δ-diketone **26** (**Scheme 1.28**).



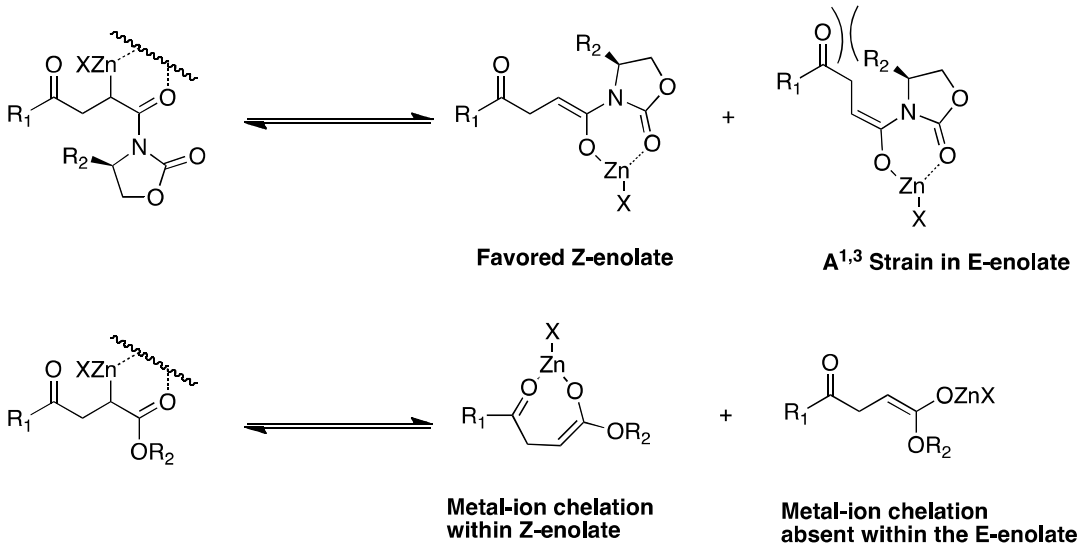
Scheme 1.28: Cyclopropanol rearrangement and ring fragmentation hypothesis

The proposed mechanisitic route illustrating the flow of events in **Scheme 3.9** will be discussed in chapter-2 of this thesis.

1.7 Tandem chain extension-aldol reaction and lactonization:

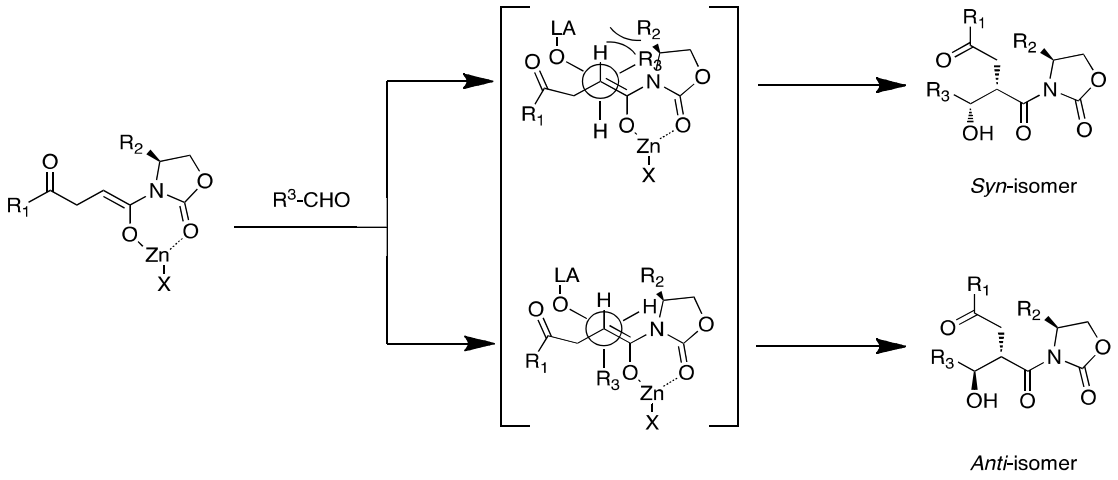
Lai[9] and Zercher reported on the diastereoselectivity of tandem chain extension-aldol reactions in β-keto substrates. They reported that tandem chain extension-aldol reaction of β-keto

esters and imides resulted in the preferential formation of the *syn*-aldol product over the *anti*-aldol product. Participation of the Z-enolate in tandem chain extension-aldol reactions of β-keto imides appeared to be favored over the E-enolate owing to the presence of $A^{1,3}$ strain observed within the E-geometry. However experimental and spectroscopic results reported by Aiken[22] for tandem chain-extension aldol reaction of β-keto esters suggested that participation of the Z-enolate results in the preferential formation of *syn*-aldol via a closed seven-membered ring transition state (**Scheme 1.29**).



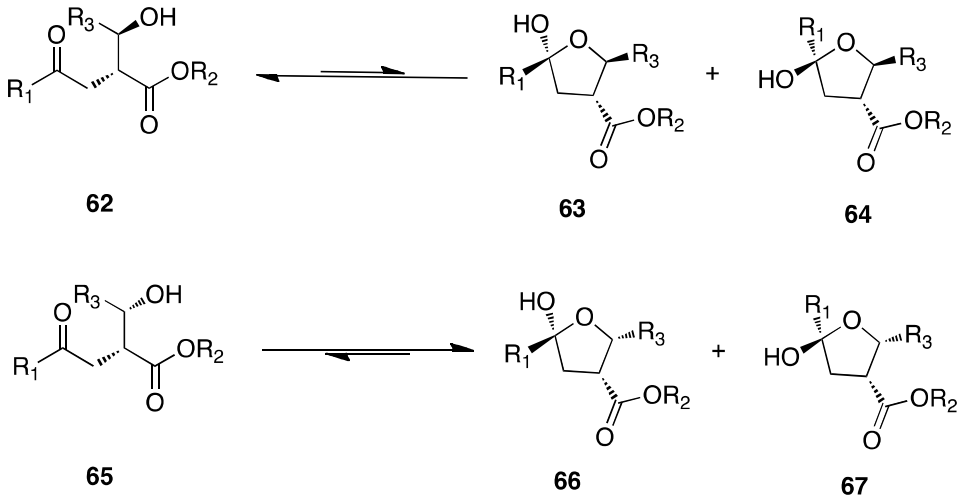
Scheme 1.29: Z and E geometries for β-keto ester and imide enolates

The formation of the *anti* aldol-isomer in β-keto imides was rationalized by the Heathcock's open-transition state model[84] where one equivalent of Lewis acid chelates to the imide carbonyl and another equivalent activates the aldehyde (**Scheme 1.30**).



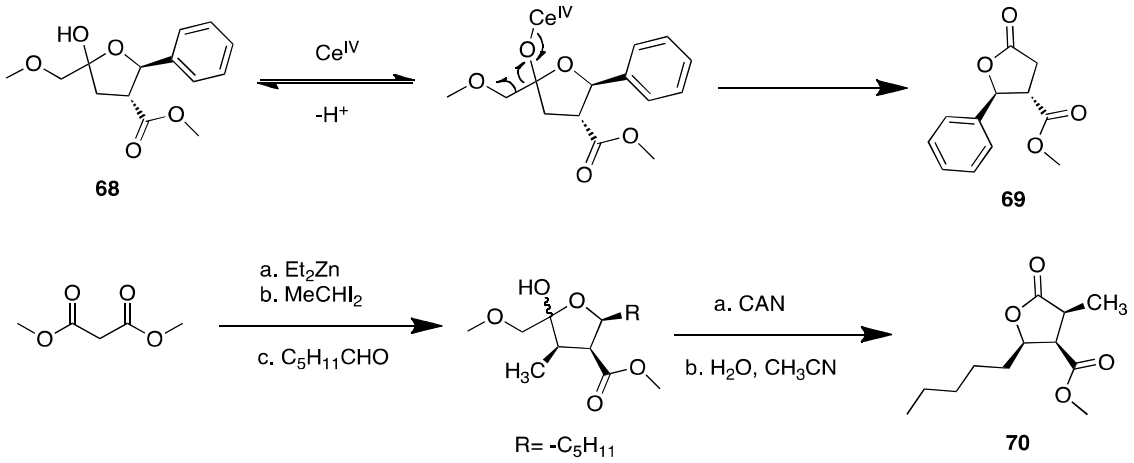
Scheme 1.30: Open transition state model for tandem chain extension-aldol reaction within β-keto imide

NMR analysis of the diastereomeric product mixture **62** and **65** resulting from the tandem chain extension aldol reaction of β-keto esters revealed that the *syn* and *anti*-isomers exist in equilibrium with their respective hemiketals **63** and **64** (*syn*-aldol) and **66** and **67** (*anti*-aldol) (**Scheme 1.31**).



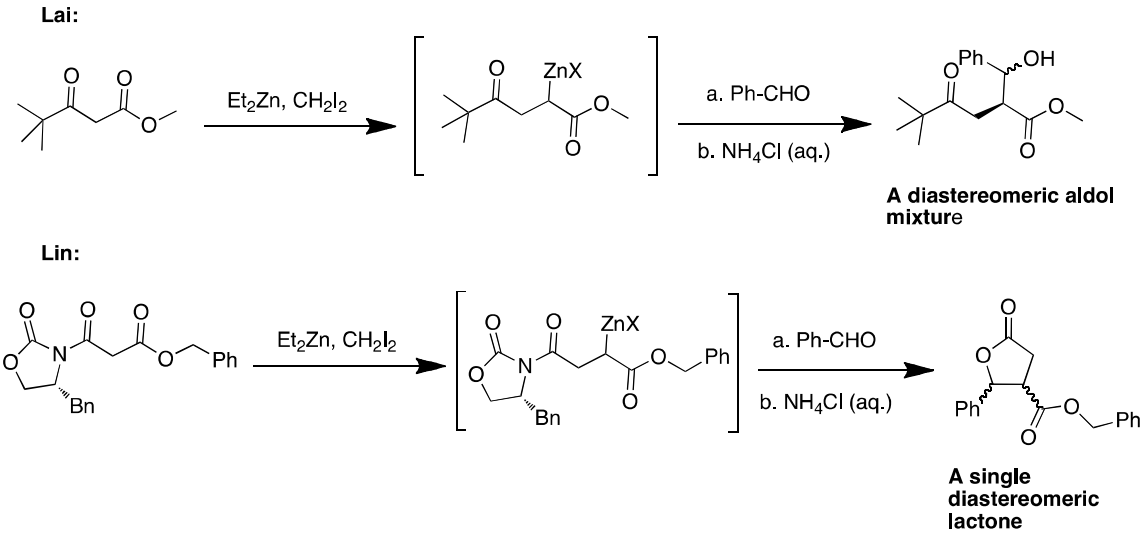
Scheme 1.31: Equilibrium between open chain and closed hemiketal isomers

Lin[60] serendipitously discovered the formation of substituted γ-lactones **69** by oxidative cleavage of the hemiketal **68** using ceric ammonium nitrate (CAN). Jacobine[69] reported that successive use of tandem chain extension-aldol reaction followed by CAN-mediated oxidative cleavage resulted in the formation of α-substituted-γ-lactones **70** (i.e. Paraconic esters) that belong to the paraconic acid family of natural products (**Scheme 1.32**).



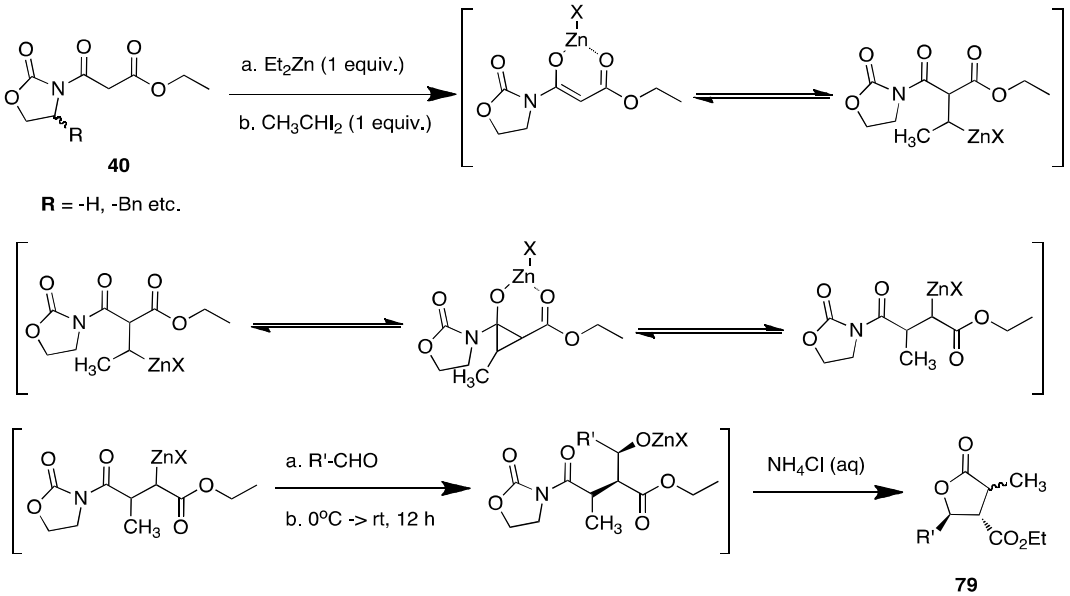
Scheme 1.32: Synthesis of substituted γ-lactones by CAN-mediated oxidative cleavage and tandem chain extension-aldol reaction

Having reported the formation of chain-extended cyclopropanols within β-keto imides (*described earlier in* **Scheme 1.4**), Lin explored the scope of zinc carbenoid-mediated homologation-cyclopropanation reaction within α-carboxyester imides. Lin reported that Furukawa carbenoid-mediated homologation-cyclopropanation within α-carboxyester imides resulted only in chain-homolgation rather than cyclopropanation. Initial studies performed on tandem chain extension-aldol (TCEA) reactions of β-keto esters[9] encouraged Lin to perform TCEA reaction using α-carboxyester imides, which resulted in the formation of a single diastereomeric γ-lactone (**Scheme 1.33**).



Scheme 1.33: Tandem chain extension-aldol reaction within β-keto esters and α-carboxyester imides

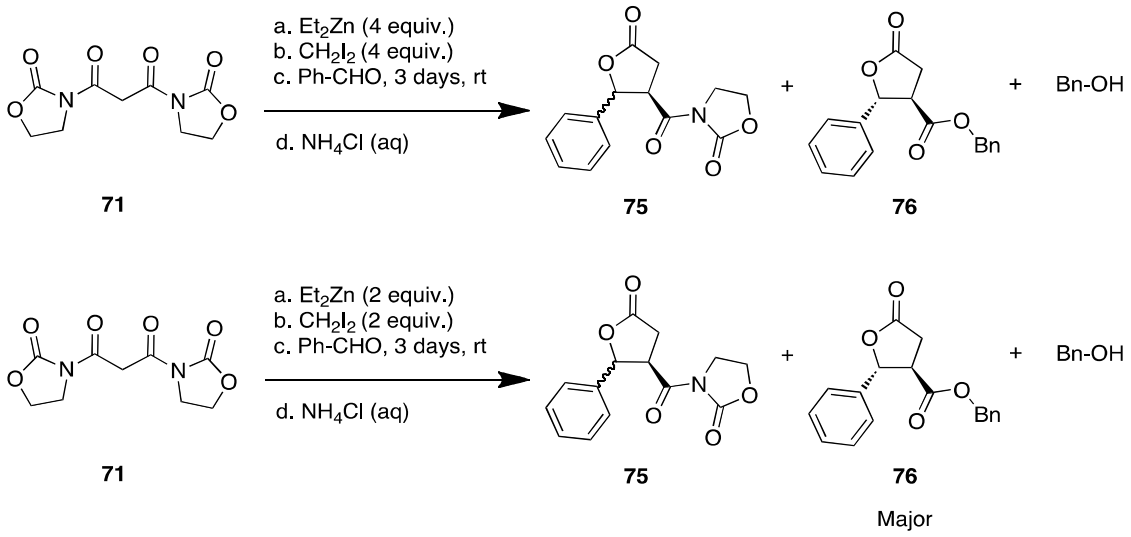
Following the influential work of Lin[60], Sadlowski[15] reported the formation of diastereomeric α-substituted-γ-lactones from **40** using zinc-carbenoids derived from 1,1-diiodoethane (**Scheme 1.34).**



Scheme 1.34: Formation of diastereomeric α-substituted-γ-lactones **79**

Both Lin[60] and Sadlowski[15] reported that the use of 1,1-diiodoethane led to the incorporation of a methyl group adjacent to the most electrophilic carbonyl functionality.

Henderson[16] reported the formation of substituted γ-lactones using benzaldehyde by varying the stoichiometry of the Furukawa's carbenoid. Henderson investigated that subjecting the malonyl bisimide **71** to 4 equivalents of the Furukawa's carbenoid results in the formation of the substituted lactones **75** and **76** along with benzyl alcohol. However subjecting the bisimide **71** to 2 equivalents of the Furukawa's carbenoid resulted in the preferential formation of **76** along with minor amounts of **75**. The formation of **76** was proposed to result from the trans-esterification of the minor diastereomer of **75** owing to the presence of benzyl alkoxide within the reaction mixture (**Scheme 1.35**).



Scheme 1.35: Zinc-mediated chain homologation of the bisimide **71** under varying carbenoid equivalents

Results obtained so far within this domain has resulted in the formation of a diastereomeric mixture of lactones with the *trans* isomers forming in increased amounts as opposed to the *cis* isomers.[15,16]

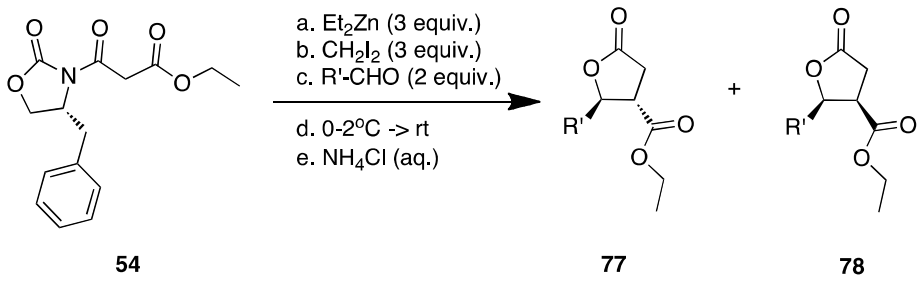
1.8 Research objective:

The goal of this research is to incrase the understanding of the cyclopropanol rearrangements (*described earlier in* **Scheme 1.17**) reported by the Zercher group. Preparation of the aryl cyclopropanol **18** and subjecting it to conditions that involve chelation of metal ions other than zinc would assess the necessity of the zinc counterion involvement. Towards this objective, commercially available β-diketone **14** would be employed and subjected to kinetically-controlled homologation-cyclopropanation reaction conditions (*described earlier in* **Scheme 1.28**) to obtain the desired aryl cyclopropanol **16**. This compound would then be subjected to a variety of base-catalyzed reaction conditions to assess the operability and selectivity of cyclopropanoxide rearrangements. Preliminary studies within the Zercher group demonstrated the rearrangement of the aryl cyclopropanol **18** to a mixture of regioisomeric cyclopropanols **16** and **18** using the bis-carbenoid [$Zn(CH_2I)_2$]. NMR analysis of the crude reaction mixture suggests that a 1 : 1 mixture of regioisomeric cyclopropanols **16** and **18** is formed under reduced reaction times.[32] It is anticipated that cyclopropanoxide rearrangement of the aryl cyclopropanol **18** could be facilitated using reaction conditions involving counter ions other than zinc (e.g. Na, Li, K, Mg etc).

An alternative approach would involve executing the rearrangement in the presence of a catalytic amount of Lewis acid (e.g. diiodozinc – ZnI_2), using non-metallic or non-nucleophilic bases [e.g. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), N,N-diisopropylethylamine (Hunig's base)]. Deprotection of a t-butyldimethylsilyl (TBDMS) ether of the aryl cyclopropanol **18** using a fluoride ion (F^-) source (e.g. tetra-n-butylammonium fluoride – TBAF) in the presence or absence of a Lewis acid should also be probed. Secondly, it would be interesting to examine ring

fragmentation reactions, since both regioisomeric cyclopropanols (**16** and **18**) could undergo ring cleavage under the right reaction conditions.

Another objective as a part of this research endeavor would be to understand the tandem chain homologation-aldol reaction and lactonization of α-carboxyester imide **54** using different aldehydes and to characterize the formation of diastereomeric mixture of lactones **77** and **78** (**Scheme 1.36**).



54 **77** **78**

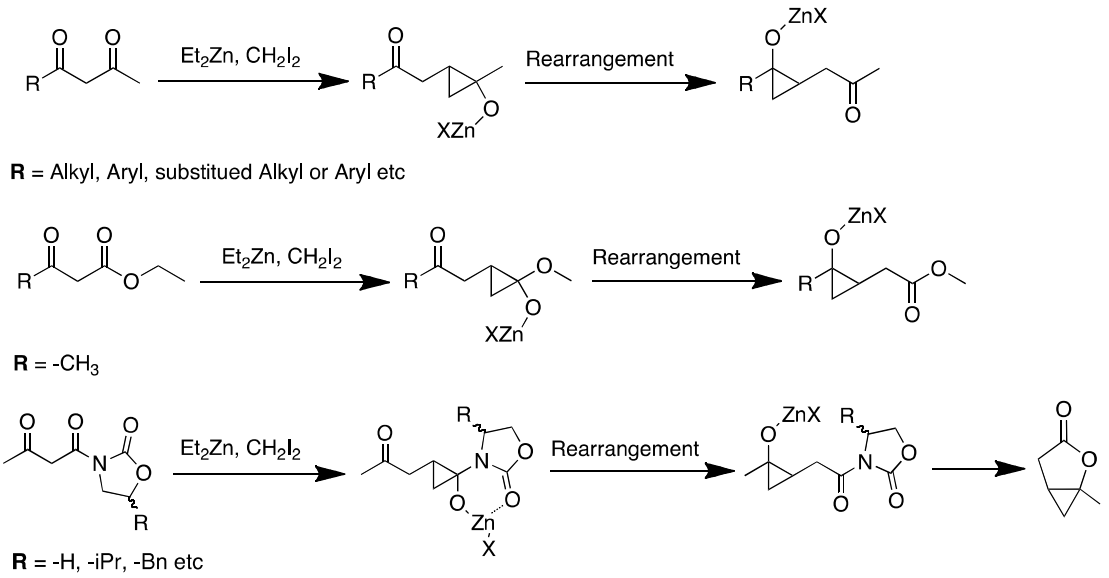
Scheme 1.36: Tandem chain extension aldol reaction and lactonization of α-carboxyester imide **54**

An investigation of the conditions (e.g. influence of chiral auxiliary within the substrate, change in the concentration of reactants / reagents and change in temperature.) that could influence the preferential formation of one diastereomeric lactone over the other would also be undertaken.

Chapter 2

Homologation-Cyclopropanation and Ring Fragmentation in β-Diketones

Homologation-cyclopropanation reactions have been extensively investigated within the Zercher group using a wide range of substrates, which include β-keto esters,[9,11] β-diketones[32,57] and β-keto imides.[14,17,26] Formation of the regioisomeric γ-keto cyclopropanols within the traditional homologation-cyclopropanation reaction was rationalized in accordance with the following explanations: a). Cyclization of the initial homoenolate to form the donor-acceptor cyclopropane intermediate determines the *regioselectivity* of the final product. b). Formation of the chain extended γ-keto cyclopropanoxide results from the nucleophilic activity of a second homoenolate. This initially formed γ-keto cyclopropanoxide could undergo further rearrangement to yield a regioisomeric cyclopropanoxide, which could be trapped either as its trimethylsilyl (TMS) ether by treatment with chlorotrimethylsilane (TMSCl) or alcohol by using a mild proton source.[26,32,34,35] Cyclopropanoxide rearrangements have been observed in cyclopropanols generated from β-keto imides[26,34,35] as well, however the final product obtained in that reaction is a cyclic lactone (**Scheme 2.0**).[26,35]



Scheme 2.0: Rearrangement of β-diketone, β-keto ester and β-keto imide derived cyclopropanoxides

2.1 Homologation-cyclopropanation and ring fragmentation (HCRF) reaction:

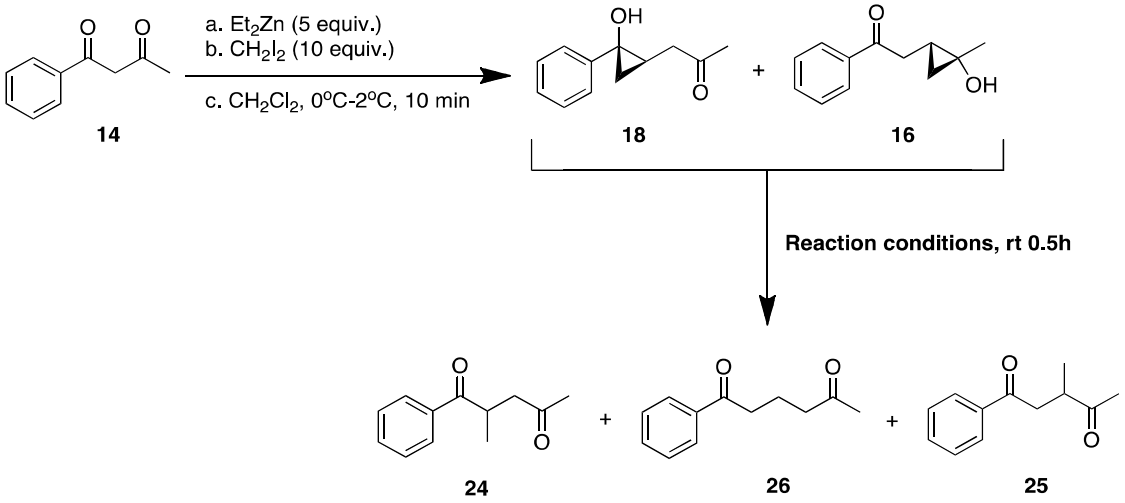
As noted earlier in **Scheme 1.16**, Xue and co-workers[31] reported that that homologation-cyclopropanation of the aryl diketone **14** resulted in the formation of the methyl cyclopropanol **16** as the major product as opposed to a time-dependent distribution of regioisomeric cyclopropanols **18** and **16** that was observed within the Zercher group.

To identify the general nature of this rearrangement mechanism, the commercially available aryl diketone **14** was procured and subjected to chain homologation-cyclopropanation conditions for 1 h as described earlier to form the aryl cyclopropanol **18**. A short reaction time was chosen to minimize the potential for rearrangement. These conditions are termed *kinetically-controlled* for the purpose of the study. As expected, the regioisomeric cyclopropanoxides (i.e. *conjugate bases of* **16** and **18)** were detected in the crude reaction mixture in a 3 : 1 ratio. The use of reduced reaction times enhanced the opportunity to isolate the aryl cyclopropanol **18** that was

previously unobserved by Xue and co-workers. Zercher group members[32] reported that aryl cyclopropanoxide **18** rearranges under extended reaction times to yield a 9 : 1 mixture of the regioisomeric cyclopropanols **16** and **18.**

NMR analysis of the crude reaction mixture depicted the formation of other products along with the regioisomeric cyclopropanols **18** and **16**. Purification of the crude reaction mixture by column chromatography and NMR analysis of the isolated fractions revealed the formation of the α-methyl-γ-diketone **25**, β-methyl-γ-diketone **24** and the chain extended δ-diketone **26** as byproducts of the reaction.

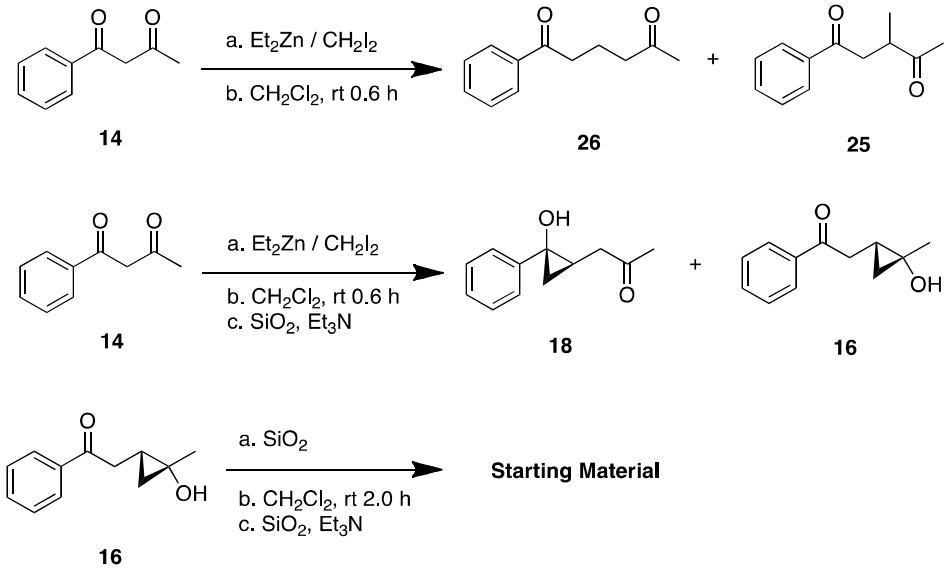
The formation of **25** and **26** in the crude reaction mixture was consistent with the observations reported by Li and co-workers[38] for acid-catalyzed ring cleavage of the methyl cyclopropanol **16 (Scheme 2.1).**



Scheme 2.1: Proposed cyclopropanoxide rearrangement of β-diketone **14** followed by ring fragmentation

Risatti[57] reported that homologation-cyclopropanation of the aryl diketone **14** using the Furukawa's carbenoid ($EtCH_2ZnI$) resulted in the formation of a 1 : 1 mixture of the chain

extended δ-diketone **26** and the α-methyl-γ-diketone **25**. The products **25** and **26** were believed to result from ring opening of the methyl cyclopropanol **16** during column chromatography; however repeating the experiment a second time followed by purification using silica conditioned with triethylamine (Et_3N) resulted in the formation of the regioisomeric cyclopropanols **18** and **16.** Attempts were made to observe the ring fragmentation of the methyl cyclopropanol **16** by stirring it under acidic conditions for 2 h (i.e. using a slurry of silica and methylene chloride); however no ring opening was observed and the starting material was found intact (**Scheme 2.2**).



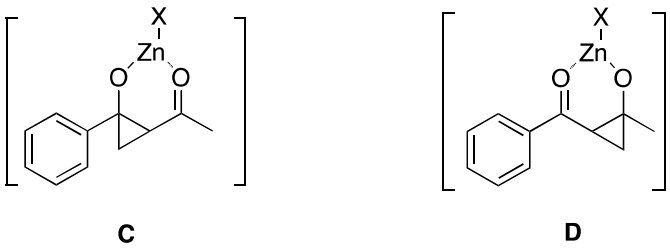
Scheme 2.2: Homologation-cyclopropanation of the aryl diketone **14** using Furukawa's carbenoid ($EtCH_2ZnI$)

Risatti reported that conditions resulting in ring fragmentation of the regioisomeric cyclopropanols **18** and **16** to yield **25** and **26** were unknown.

It was however investigated that homologation-cyclopropanation of the aryl diketone **14** using bis-carbenoid [$Zn(CH_2I)_2$] included the formation of β-methyl-γ-diketone **24** within the

crude reaction mixture, which was consistent with acid or base-mediated ring cleavage of the aryl cyclopropanoxide **18** during the homologation-cyclopropanation reaction. It is worth noting that formation of the β-methyl-γ-di ketone **24** was not observed and reported by Li and co-workers (**Scheme 3.6**). This might be due to the fact that regioisomeric methyl cyclopropanol **16** formed as the major product during homologation-cyclopropanation was individually isolated and the byproducts were never observed.

Zercher group members believed that the formation of the regioisomeric cyclopropanols **16** and **18** could be resulting through the intermediacy of two donor-acceptor cyclopropane intermediates **C** and **D** (**Figure 5)**.



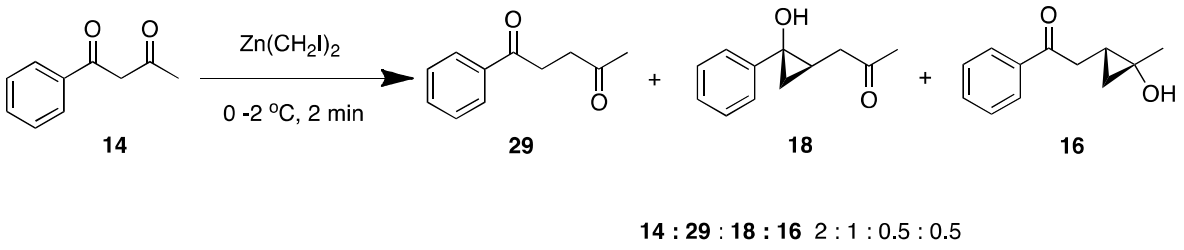
C **D**

Figure 5: Proposed structures of two possible donor-acceptor cyclopropane intermediates **C** and **D** for the aryl diketone **14**

This was confirmed by subjecting the aryl diketone **14** to homologation-cyclopropanation conditions and sampling the reaction mixture at different time intervals to observe the dynamics of the reaction. The reaction was monitored over a period of 12 h by thin-layer chromatography (TLC) and individual aliquots of the crude reaction mixture were worked up, extracted and analyzed by NMR (Nuclear Magnetic Resonance) spectroscopy.

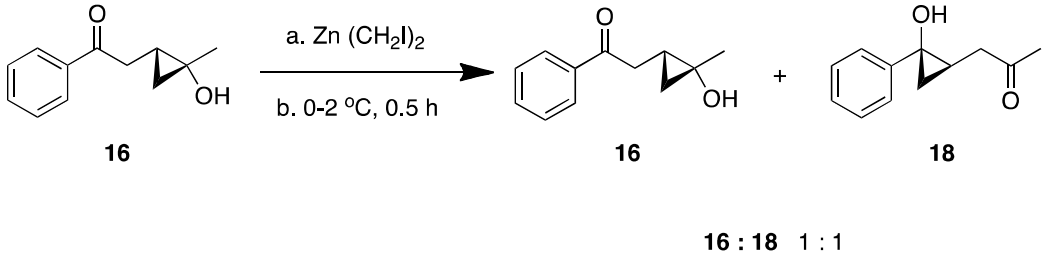
2.2 Mechanistic investigation of HCRF reaction under reduced reaction times:

Initial results obtained for the 2-minute crude reaction mixture stirred under ice-cold conditions confirmed the presence of the unreacted aryl diketone **14**, the chain extended γ-diketone **29** along with minor amounts of the regioisomeric cyclopropanols **16** and **18** (**Scheme 2.3**).



Scheme 2.3: Initial results for homologation-cyclopropanation of β-diketone **14** using bis-carbenoid after 2 minutes

It is possible from the above results that formation of a 1 : 1 mixture of the regioisomeric cylcopropanols **18** and **16** results from the fragmentation of both the donor-acceptor cyclopropanes (**C** and **D**) at the same time. To confirm this result an attempt was made to observe the methyl cyclopropanol **16** rearrange to the aryl cyclopropanol **18** under similar reaction conditions (**Scheme 2.4**)

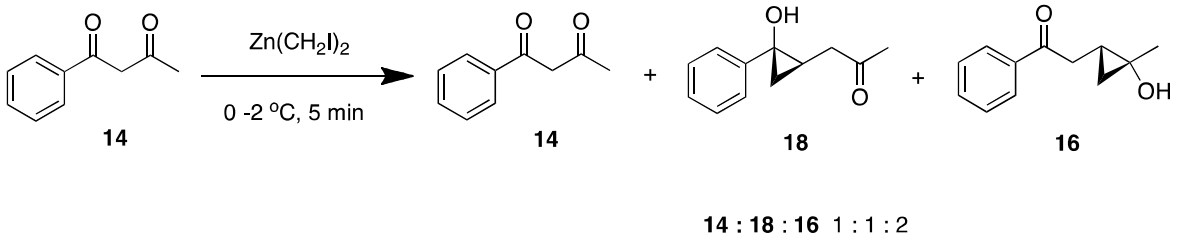


Scheme 2.4: Proposed cyclopropanoxide rearrangement of methyl cyclopropanol **16** under reduced reaction times.

Formation of a 1 : 1 mixture of the regioisomeric cyclopropanols **16** and **18** indicated the equilibration of the regioisomeric cyclopropanoxides (i.e. conjugate bases of **16** and **18**) under the reaction conditions which was termed "*Thermodynamically controlled*" for the purpose of the reaction.

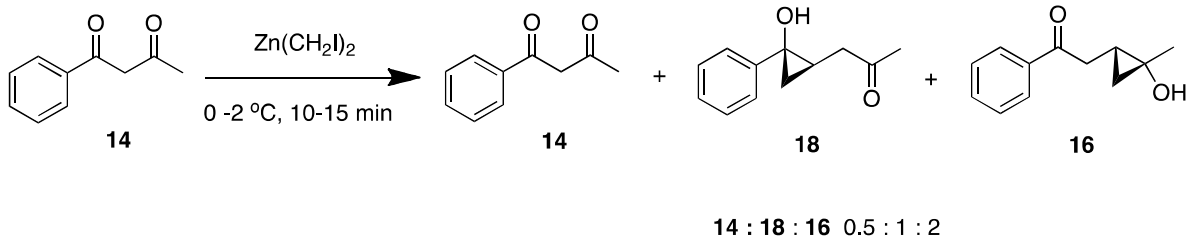
However, formation of a 1 : 1 mixture of the aryl diketone **14** and the aryl cyclopropanol **18** within the crude reaction mixture after 5 min under ice-cold conditions suggested the selective formation and fragmentation of the donor-acceptor cyclopropane **D**. Involvement of this donor-acceptor cyclopropane was hypothesized to be a result of the intermediate zinc homoenolate rapidly cyclizing into the methyl ketone as opposed to the aryl ketone which was favored due to the activation energy associated with breaking the conjugation of the latter.

Formation of a 2 : 1 mixture of the regioisomeric cyclopropanols **16** and **18** was also observed around the same time as a result of the aryl cyclopropanol **18** rearranging to the methyl cyclopropanol **16** (**Scheme 2.5**).



Scheme 2.5: Homologation-cyclopropanation of aryl diketone **14** followed by cyclopropanoxide rearrangement after 5 minutes

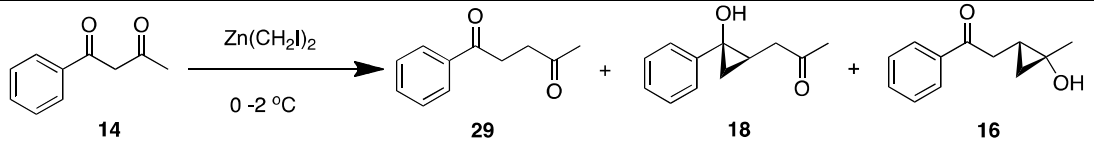
Results obtained from the 10-15 min crude reaction mixture stirred under ice-cold conditions revealed the presence of a 2 : 1 : 0.5 mixture of the regioisomeric cyclopropanols **16** and **18** along with the aryl diketone **14** (**Scheme 2.6**).



Scheme 2.6: Time-dependent distribution of the regioisomeric cyclopropanols **18** and **16** after 10-15 minutes

It is worth noticing in **Scheme 2.6** that the chain extended γ-diketone **29** was completely consumed. Zercher group members proposed that the chain extended enolate of **14** was reacting with the third equivalent of the bis-carbenoid resulting in the formation of the α-methylated enolate which in turn cyclizes into the aryl ketone yielding the aryl cyclopropanoxide **18**. The aryl cyclopropanoxide **18** then undergoes a cyclopropanoxide rearrangement resulting in a mixture of regioisomeric cyclopropanoxides **18** and **16** respectively. The overall results for homologation-cyclopropanation of the aryl diketone **14** under ice-cold conditions are summarized in **Table 1**.

Table 1: Time-dependent product distribution of γ-keto cyclopropanols **18** and **16** under ice-cold conditions and reduced reaction times

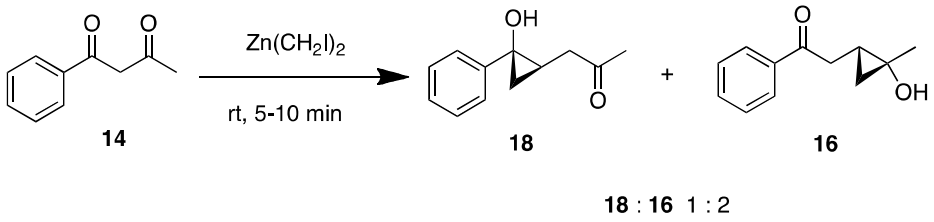


Entry	Reaction times (min)	% Composition of products			
		14	**29**	**18**	**16**
1.	2	50	25	12.5	12.5
2.	5	25	-	25	50
3.	10-15	14	-	29	57

** % composition was calculated using the combined ratios of individual products in the crude mixture*

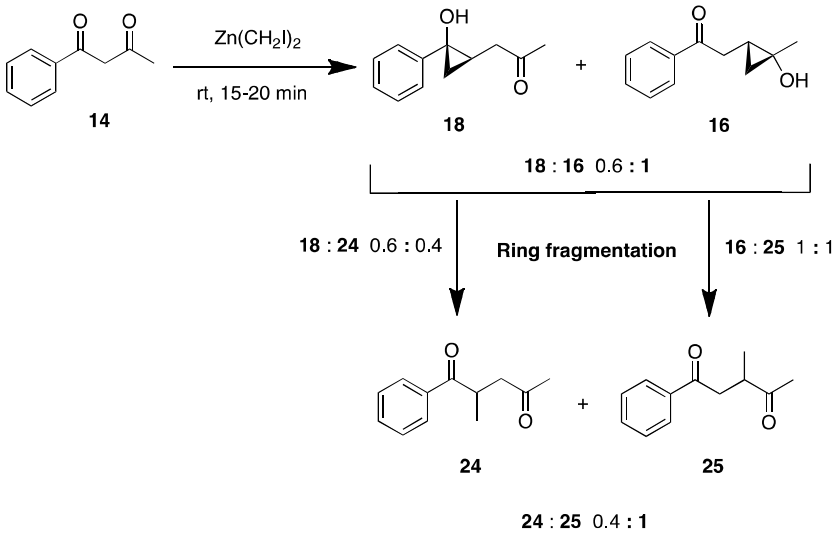
2.3 Mechanistic investigation of HCRF reaction under extended reaction times:

Further results were obtained by switching the reaction conditions. The homologation-cyclopropanation reaction was observed at room temperature for extended time periods. Initial results obtained from the crude reaction mixture stirred at room temperature for 5-10 min revealed the presence of a 2 : 1 mixture of regioisomeric cyclopropanols **18** and **16 (Scheme 2.7**).



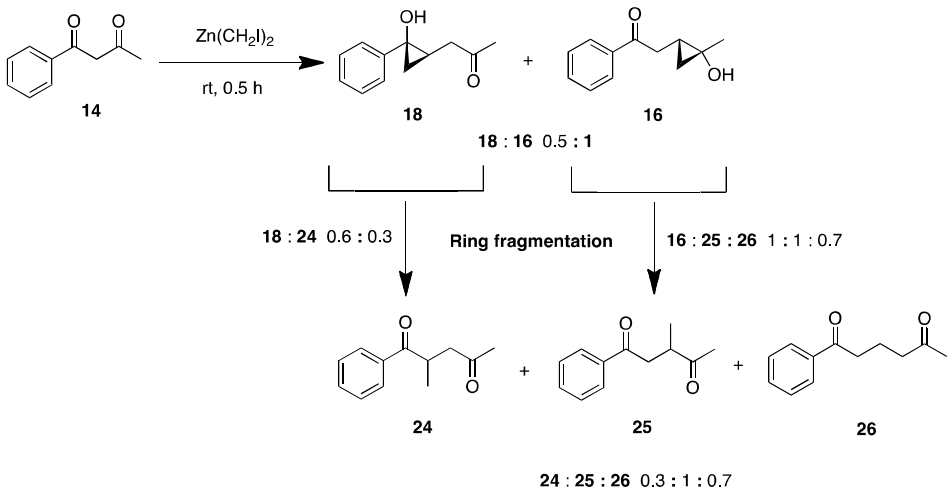
Scheme 2.7: Rearrangement of the γ-keto cyclopropanoxides **18** to **16**

However around 15-20 min, it is worth noting that the ring-fragmented homoenolate **25** was formed in a 1 : 1 ratio with the γ-keto cyclopropanol **16** while the homoenolate **24** was only seen forming in a 0.4 : 0.6 ratio with its regioisomeric γ-keto cyclopropanol **18** (**Scheme 2.8**). The fragmentation of the conjugate bases of **18** and **16** to their zinc ketone homoenolates **24** and **25** was consistent with the regioselective ring opening of cyclopropanols by the use of organozinc reagents and Lewis acids (e.g. ZnI_2) as reported earlier in **Scheme 1.27**.[38,57]



Scheme 2.8: Ring fragmentation of regioisomeric cyclopropanoxides **18** and **16**

The results obtained for the 0.5 h crude reaction mixture revealed the presence of the regioisomeric cyclopropanols **18** and **16** along with their ring-fragmented counterparts **24** and **25**. However another product **26** was seen forming within the crude reaction mixture, which was believed to arise from another kind of ring fragmentation of the methyl cyclopropanol **16**. The product was characterized by NMR and found to be the chain extended δ-diketone (i.e. *1-Phenylhexane-1,5-dione*) [**Scheme 2.9**].



Scheme 2.9: Ring fragmentation and homoketonization of methyl cyclopropanoxide **16**

The formation of the chain extended δ-diketone **26** along with the α-methylated-γ-di ketone **25** in a 0.7 : 1 ratio suggested that two different modes of ring fragmentation were operational within the regioisomeric cyclopropanoxide **16** (**Figure 6**).

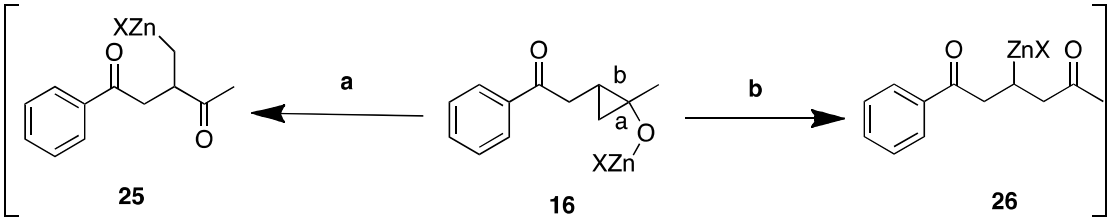


Figure 6: Two modes of ring fragmentation within methyl cyclopropanoxide **16**

However it was observed that ring fragmentation of the methyl cyclopropanoxide **16** slightly favored the formation of the α-methylated-γ-diketone **25** (i.e. *α-methylation*) over the chain extended δ-di ketone **26 (**i.e. *Homoketonization***)**. Hoyano and Patel[42] chiefly explained this based on the formation of the more stable primary carbanion in the α-methylated homoenolate **25**, which is less hindered towards protonation as opposed to the secondary carbanion, formed in the chain extended δ-diketone **26**. Also it is worth noting in **Scheme 2.9** that *homoketonization* resulting in **26** was occurring almost in a 1 : 1 ratio with *α-methylation* resulting in **25** (**Figure 7**).[36,37,42,43]

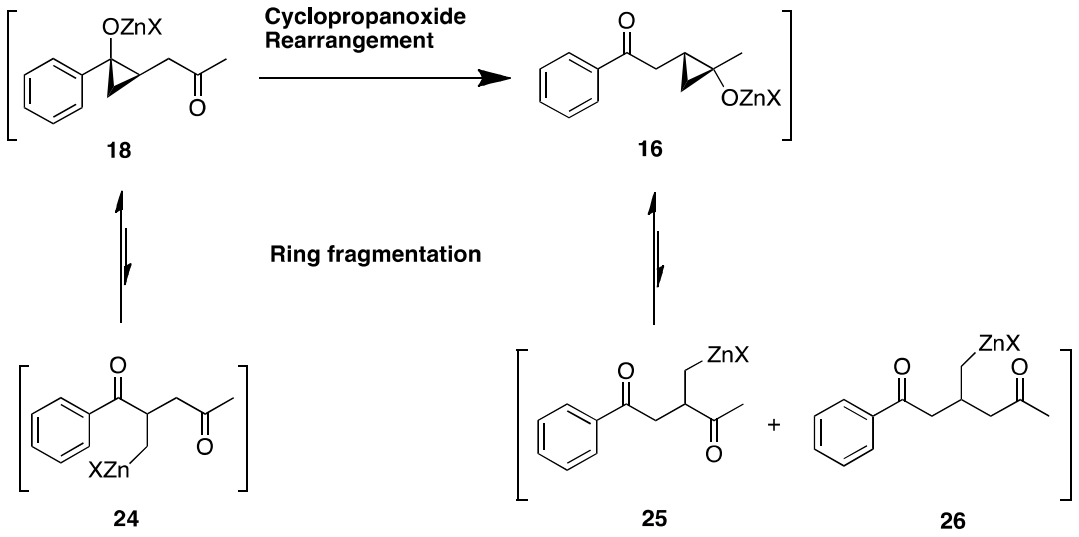
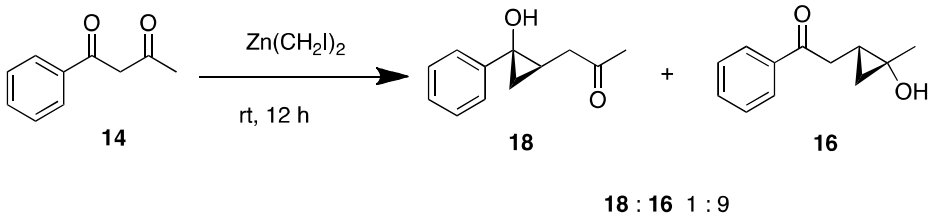


Figure 7: Proposed mechanism resulting in the formation of methyl cyclopropanol **16** from ring fragmented homoenolates **24**, **25** and **26**

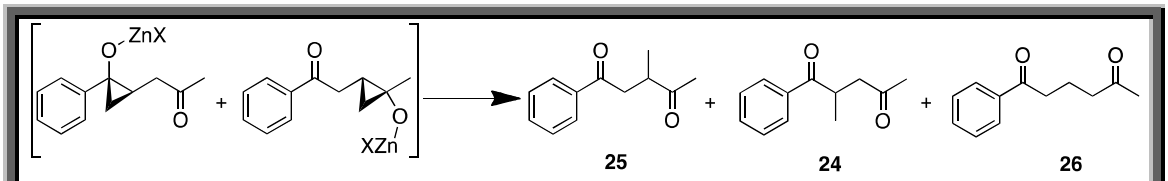
Results obtained from the crude reaction mixture over a period of 12 h revealed only the presence of a 9 : 1 mixture of the regioisomeric cyclopropanols **16** and **18** (**Scheme 2.10**). This observation was consistent with the results obtained for the time-dependent distribution of γ-keto cyclopropanols as reported by Mower (**Scheme 1.17**).



Scheme 2.10: Formation of the methyl cyclopropanol **16** as the major product

The overall results for cyclopropanoxide rearrangements followed by ring fragmentation during the zinc-mediated homologation-cyclopropanation reaction are illustrated in **Table-2.**

Table-2: Bis-carbenoid mediated time dependent HCRF reaction

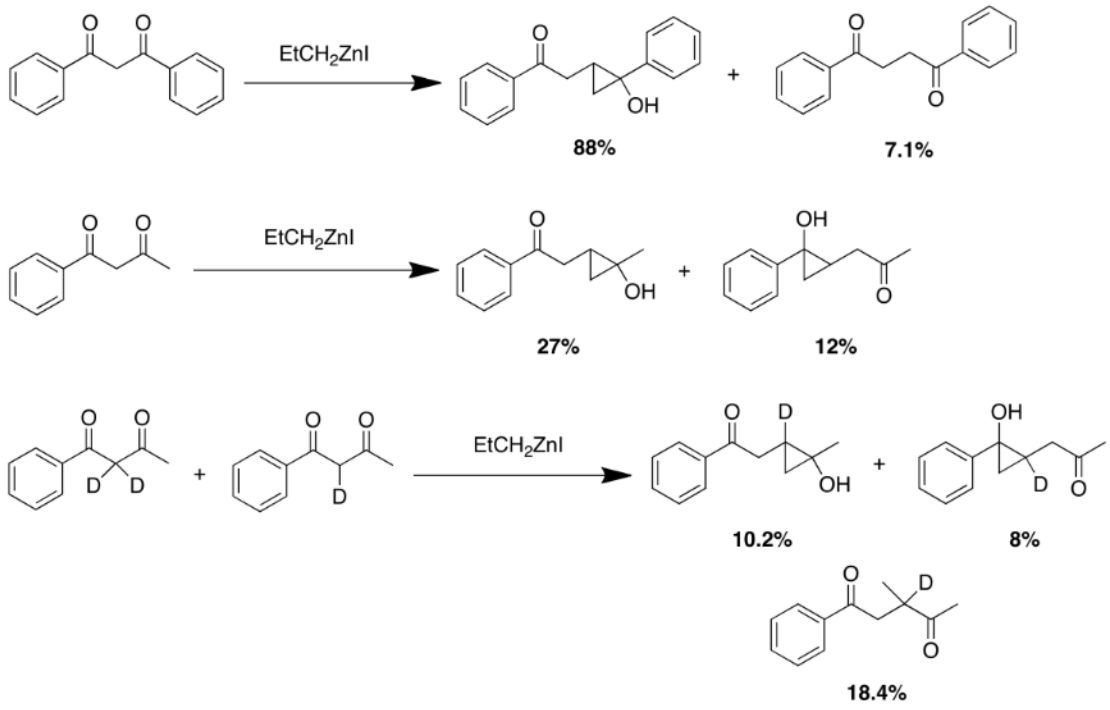


Entry	Reaction times (h)	% Composition of Cyclopropanols		% Composition of products		
		18	**16**	**24**	**25**	**26**
1.	0.5	13	25	8	25	18
2.	5	25	75	-	-	-
3.	12	10	90	-	-	-

** % composition was calculated using the combined ratios of individual products in the crude mixture*

It is worth noting that the ring-fragmented byproducts: α-or β-methylated-γ-diketones (i.e. **24** and **25)** and the chain extended δ-diketone **26** were never observed in the 12 h crude reaction mixture although they were characterized within the 0.5 h crude reaction mixture (*as described earlier in* **Scheme 2.9**). These results are surprising and emphasize that further experimental investigation is mandated to identify the dynamics of the homologation-cyclopropanation reaction.

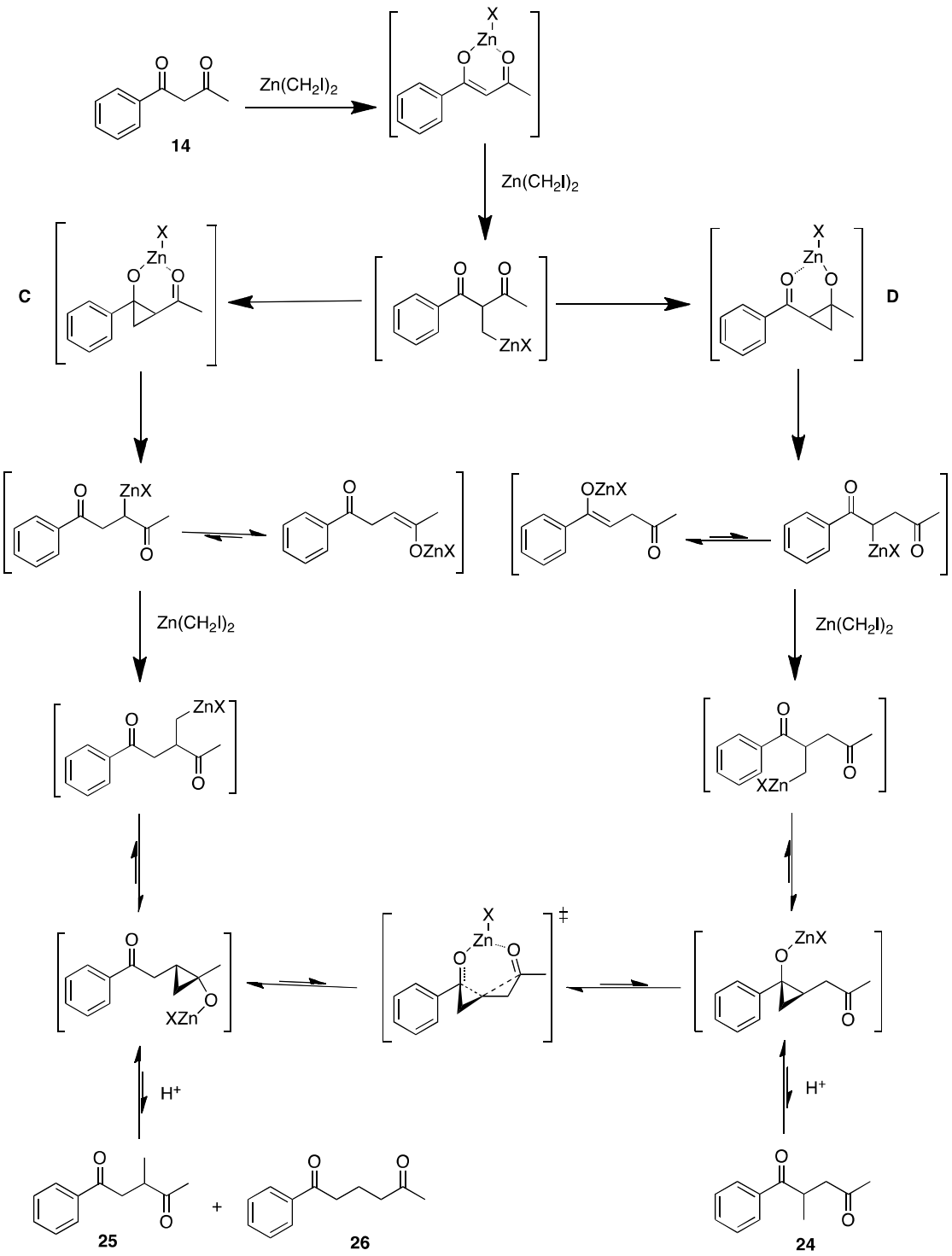
Risatti[57] determined that homologation-cyclopropanation within aryl diketones using Furukawa's carbenoid resulted in the formation of the regioisomeric cyclopropanoxides, which was followed by ring fragmentation. Deuterium labeled studies on homologation-cyclopropanation of aryl diketones also supported the evidence of ring fragmentation of the methyl cyclopropanoxide to the α-methylated-γ-di ketone **25** (**Scheme 2.11**).



Scheme 2.11: Initial results for homologation-cyclopropanation in aryl diketones and deuterium labeled homologation-cyclopropanation and ring fragmentation studies

2.4 Proposed mechanism for the HCRF reaction:

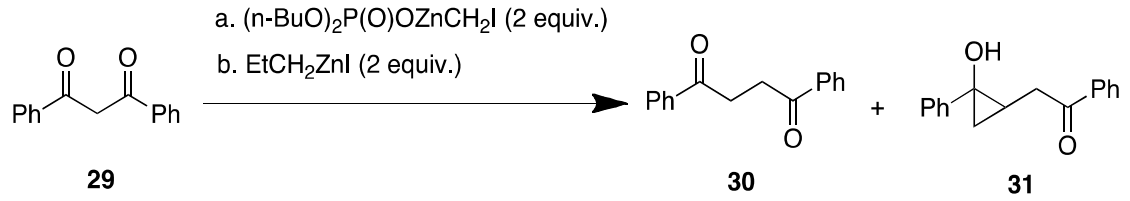
The proposed mechanism for homologation-cyclopropanation reaction of the aryl diketone **14** is described in **Scheme 2.12**. The mechanism involves the participation of the donor-acceptor cyclopropanes **C** and **D**. Formation of ring-fragmented products **24**, **25** and **26** was attributed to the equilibration of the regioisomeric cyclopropanoxides to their respective homoenolates.



Scheme 2.12: Proposed mechanism for homologation-cyclopropanation and ring fragmentation of β-diketones

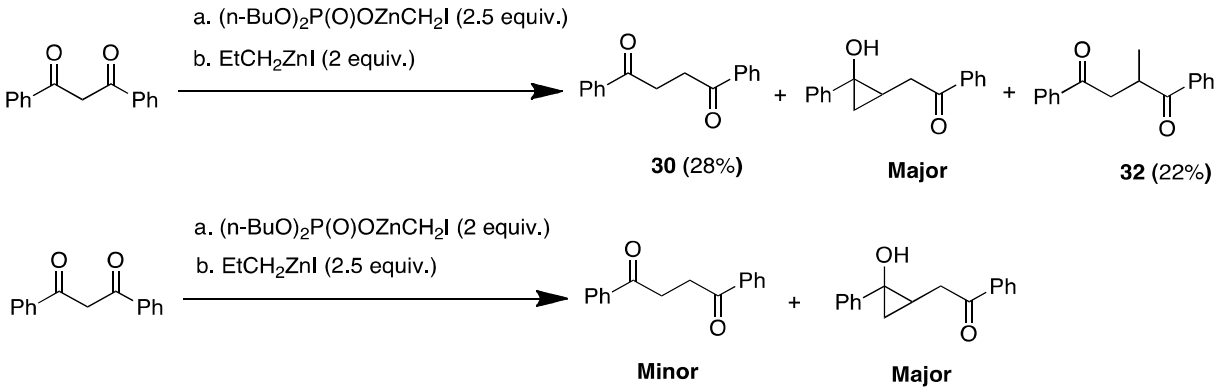
2.5 Homologation-cyclopropanation in β-Diketones using mixed carbenoids:

Inspired by initial contributions made by Zercher and co-workers towards the traditional chain extension mechanism[7], Voituriez et al[44] proposed a similar mechanism for homologation-cyclopropanation using a *mixed carbenoid*. The carbenoid mixture was prepared using a combination of Charette's carbenoid i.e. Iodomethyl zinc di-n-butyl phosphonate [$(nBuO)_2P(O)OZnCH_2I$] and Furukuwa's carbenoid ($EtZnCH_2I$).[45] He reported that subjecting the β-diketone **29** under the reaction conditions using just Charette's carbenoid [$(nBuO)_2P(O)OZnCH_2I$] resulted in the preferential formation of the chain extended γ-diketone **30.** However using equivalent proportions of Charette's carbenoid [$(nBuO)_2P(O)OZnCH_2I$] and the Furukuwa's carbenoid ($EtZnCH_2I$) resulted in the preferential formation of the γ-keto cyclopropanol **31** along with minor amounts of the chain extended γ-diketone **30** (**Scheme 2.13**).



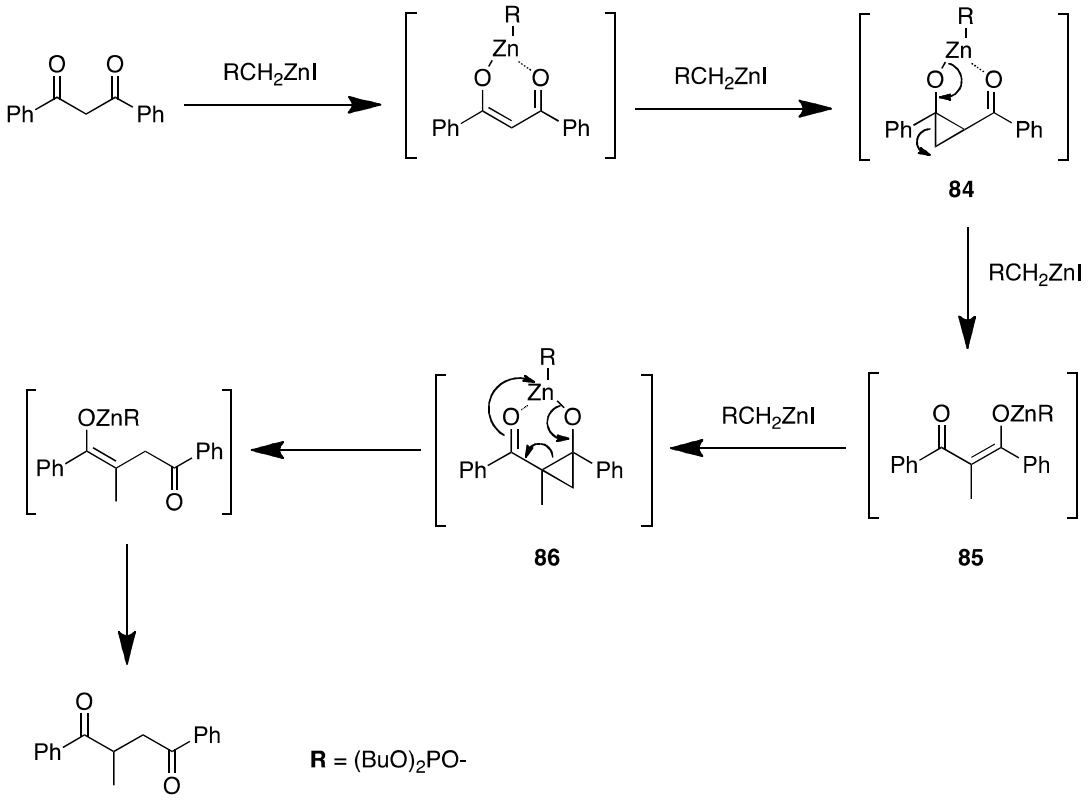
Scheme 2.13: Homologation-cyclopropanation of β-diketone **29** using a combination of Charette's carbenoid and Furukawa's carbenoid

Voituriez et al. reported that presence of excess Furukawa's carbenoid ($EtZnCH_2I$) within the carbenoid mixture preferentially yielded the γ-keto cyclopropanol **31**. On the contrary, excess Charette's carbenoid [$(nBuO)_2P(O)OZnCH_2I$] within the carbenoid mixture resulted in the formation of the α-methyl-γ-diketone **32** and the chain extended γ-diketone **30** in equal proportions along with increased yields of the γ-keto cyclopropanol **31** (**Scheme 2.14**).



Scheme 2.14: Product distributions based on carbenoid composition

The formation of the α-methyl-γ-diketone **32** was attributed towards the unfavorable ring opening of the initial donor-acceptor cyclopropane intermediate followed by a second cyclopropanation / ring opening sequence using the phosphonate carbenoid as described in **Scheme 2.15**. The proposed mechanism involves the formation of the donor-acceptor cyclopropane intermediate **84** followed by its subsequent fragmentation to the initial homoenolate. This initial homoenolate then reacts with a second equivalent of the Charette's carbenoid to form the α-methylated enolate **85**, which then reacts with a third equivalent of the Charette's carbenoid to form another donor-acceptor cyclopropane intermediate **86**. Fragmentation of this donor-acceptor cyclopropane intermediate results in the formation of the chain-extended α-methylated enolate, which on mild acidic workup leads to the formation of the α-methylated-γ-diketone.



Scheme 2.15: Homoglation-cyclopropanation and ring fragmentation in β-diketones using mixed carbenoids

This mechanistic rationale proposed by Voituriez et.al. was not in agreement with the results reported by Lin and Zercher[14] for homologation-cyclopropanation of α-substituted β-keto esters, phosphonates and imides.[13,14,46] The primary difference is the alternate fragmentation of donor-acceptor cyclopropane intermediate **84** to the initial homoenolate. Computational studies performed by Eger and Zercher[30] have shown that fragmentation of the initial donor-acceptor cyclopropane intermediate to the chain extended enolate has an energy barrier of 3-4 kcal/mol, which is likely to be faster than the alternate cleavage mechanism proposed by Voituriez, that would regenerate the initially formed homoenolate (**Figure 8**).

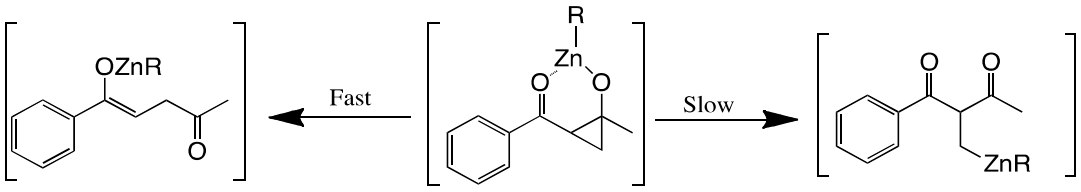


Figure 8: Original results for carbenoid insertion and chain homologation

In addition, formation of the α-methylated enolate **85** would require a proton source prior to reacting with the second equivalent of the Charette's carbenoid.

In summary, the one–pot homologation-cyclopropanation and ring fragmentation (HCRF) of β-diketones has not been reported previously. We report herein that the HCRF reaction of the aryl diketone **14** with bis(iodomethyl)zinc results in the formation of the α-and β-methylated-γ-diketones **24** and **25**, respectively, which is believed to occur through the ring fragmentation of the regioisomeric cyclopropanoxides (i.e. *conjugate bases of* **18** and **16)**. The formation of the β-methylated-γ-diketone **24** provides evidence of the involvement of the donor-acceptor cyclopropane **D** within the homologation-cyclopropanation reaction.

2.6 Results and Discussion:

Ring fragmentations of tertiary cyclopropanols have been widely explored over the years and are analogously compared to homoenols in equilibrium with their corresponding aldehydes or ketones.[40,48,55] Initial studies on ring fragmentation within regioisomeric cyclopropanols have indicated that ring cleavage occurs more readily towards the ring carbon atom which can best stabilize a negative charge.[42,55] Cleavage of *trans*-1,2-disubstituted aryl cyclopropanols under both acidic and basic conditions have been widely reported and studied.[36,42] However the one-pot chemistry of homologation-cyclopropanation in β-diketones followed by ring fragmentation (HCRF) using bisiodomethyl zinc [$Zn(CH_2I)_2$] has not been reported previously. We report

herein that HCRF reaction of the aryl diketone **14** under *kinetically-controlled* conditions resulted in preferential formation of the aryl cyclopropanoxide **18** within the crude reaction mixture. When longer reaction times are applied preferential formation of the methyl cyclopropanol **16** occurs.

Increased amounts of aryl cyclopropanol **18** are believed to result from the fragmentation of the preferentially formed donor-acceptor cyclopropane intermediate **D**. Formation of the methyl cyclopropanol **16** is believed to result from the fragmentation of the donor-acceptor cyclopropane intermediates **C** and **D**. Formation of **16** through **C** involves the intramolecular cyclization of the α-methylated zinc homoenolate **25** into the carbonyl containing the methyl ketone, while formation of **16** through **D** involves a cyclopropanoxide rearrangement of the aryl cyclopropanol (i.e. *conjugate base of* **18**).

Product formation from both **C** and **D** were operational; however preferential formation of the aryl cyclopropanoxide (i.e. conjugate base of **18**) within the crude reaction mixture as opposed to the α-methylated zinc homoenolate **25** suggests a preference for the donor-acceptor cyclopropane intermediate **D**. This led us to conclude that formation of **16** was arising primarily through a *cyclopropanoxide rearrangement* (**Figure 9**).

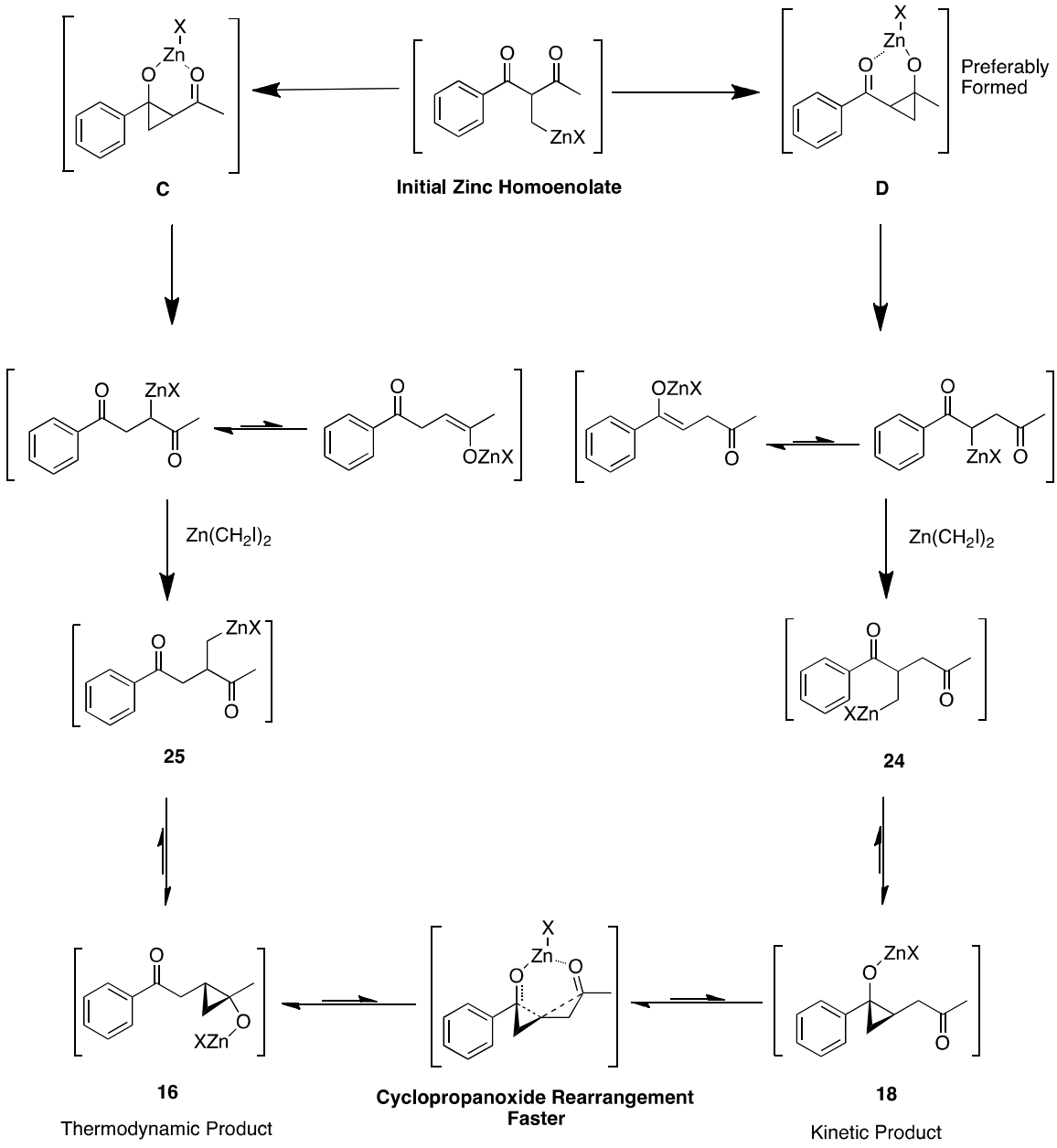


Figure 9: Proposed formation of **16** via two donor-acceptor cyclopropane intermediates **C** and **D**

NMR results for the zinc-mediated homologation-cyclopropanation reaction revealed the formation of both **25** and **26** within the crude reaction mixture. The fragmentation of methyl

cyclopropanoxide (i.e. *conjugate base of* **16**) to **25** and **26** was governed by the relief of ring strain (**Figure 10**).

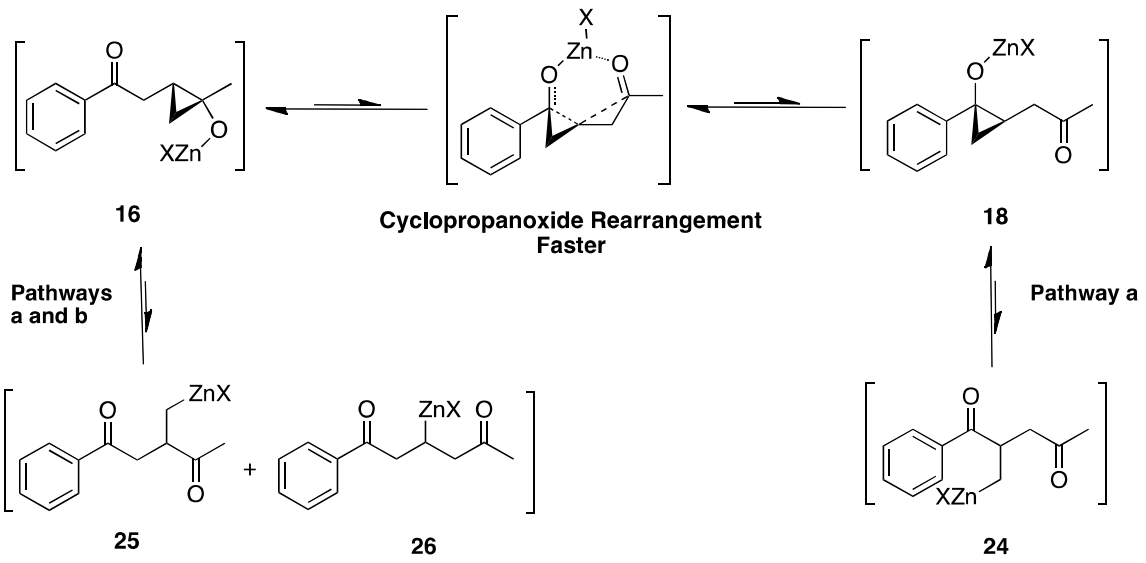


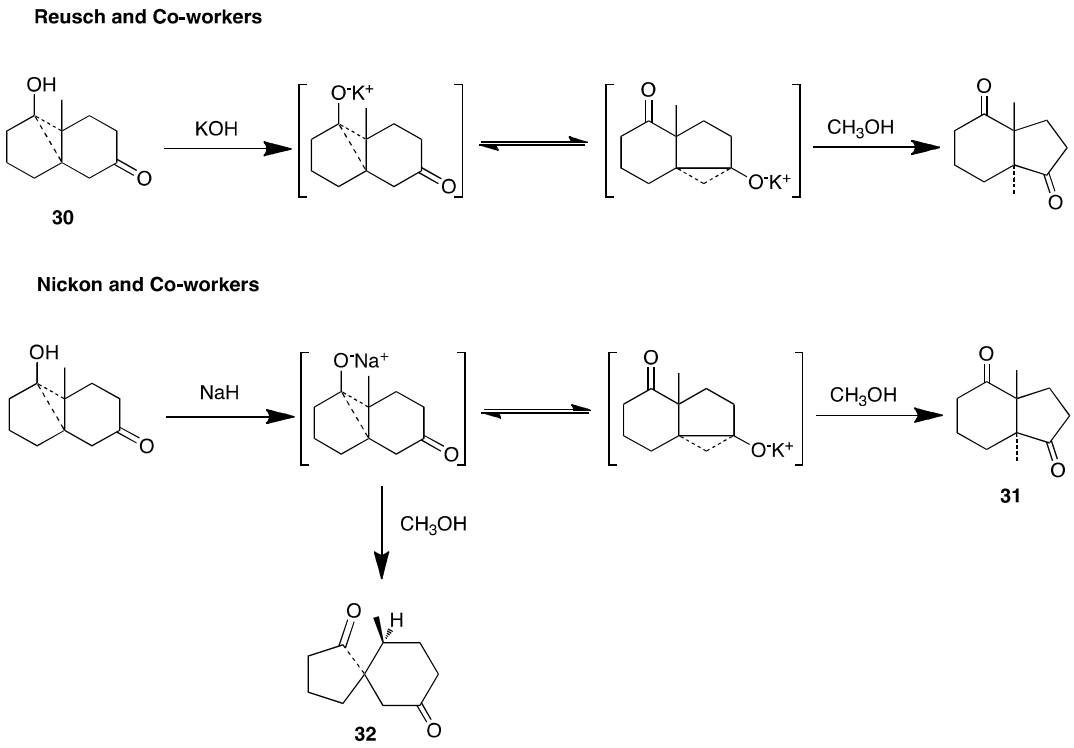
Figure 10: Ring fragmentation pathways for the regioisomeric cyclopropanoxides (i.e. *conjugate bases of* **18** and **16**)

The formation of minor amounts of **24** was ascertained by the ring fragmentation of the aryl cyclopropanoxide (i.e. conjugate base of **18**) however, evidence for the formation of **26** from the ring fragmentation of aryl cyclopropanoxide (i.e. conjugate base of **18**) was not observed. This may be due to appearance of the *cyclopropanoxide rearrangement* that involves cleavage of the bond required to form the chain-extended δ-diketone **26**.

Chapter 3

Selectivity within Aryl Cyclopropanoxide Rearrangements

Reusch[47] and Nickon[41] reported the base-catalyzed rearrangement and ring cleavage of γ-keto cyclopropanols **30** within bicyclic ring systems using potassium hydroxide (KOH) and sodium hydride (NaH) respectively (**Scheme 3.0**). Cyclopropanoxide rearrangements were rationalized in terms of, "*equilibrating γ-keto cyclopropanoxides under the reaction conditions and solvent capture of the more stable one*".[42]



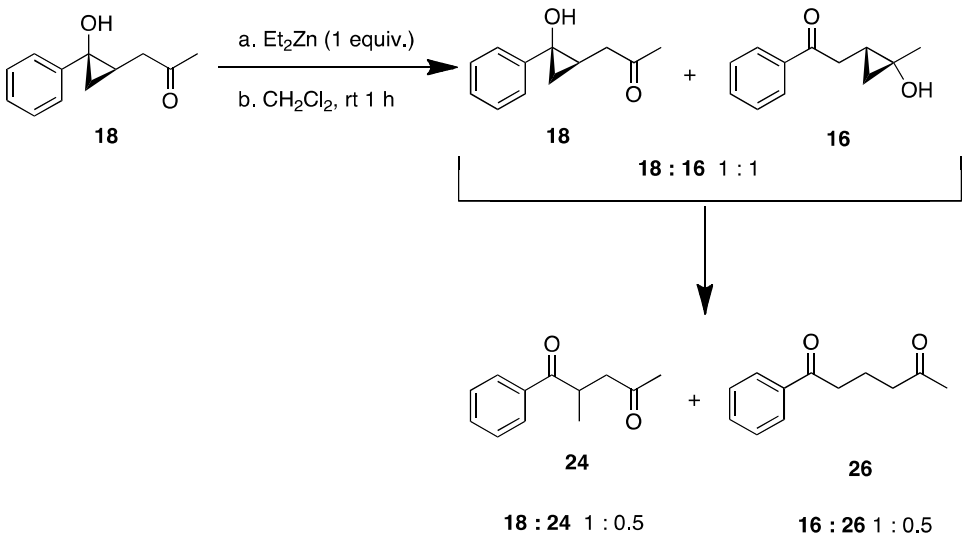
Scheme 3.0: Base catalyzed cyclopropanoxide rearrangements and ring cleavage

They suggested that a base-catalyzed cyclopropanol rearrangement could be effected by converting **30** into its metal alkoxide (salt) followed by subsequent quenching with methanol to yield the α, β-methylated-γ-diketone **31**. However Nickon also reported the formation of the unexpected spiroketone **32** by an alternate ring fragmentation pathway of the initially formed regioisomeric cyclopropanoxide followed by retention of configuration in the protonation step.

The general nature of cyclopropanoxide rearrangements were established within the Zercher group by individually isolating the aryl cyclopropanol **18** and subjecting it to bis-carbenoid [$Zn(CH_2I)_2$] to obtain a mixture of regioisomeric cyclopropanols **18** and **16.**[32] However, formation of the α- and β-alkylated-γ-diketones as well as the chain extended δ-diketone within the chain homologation-cyclopropanation reaction provides us the opportunity to expand the scope of the chain-extension methodology.[39,42,48]

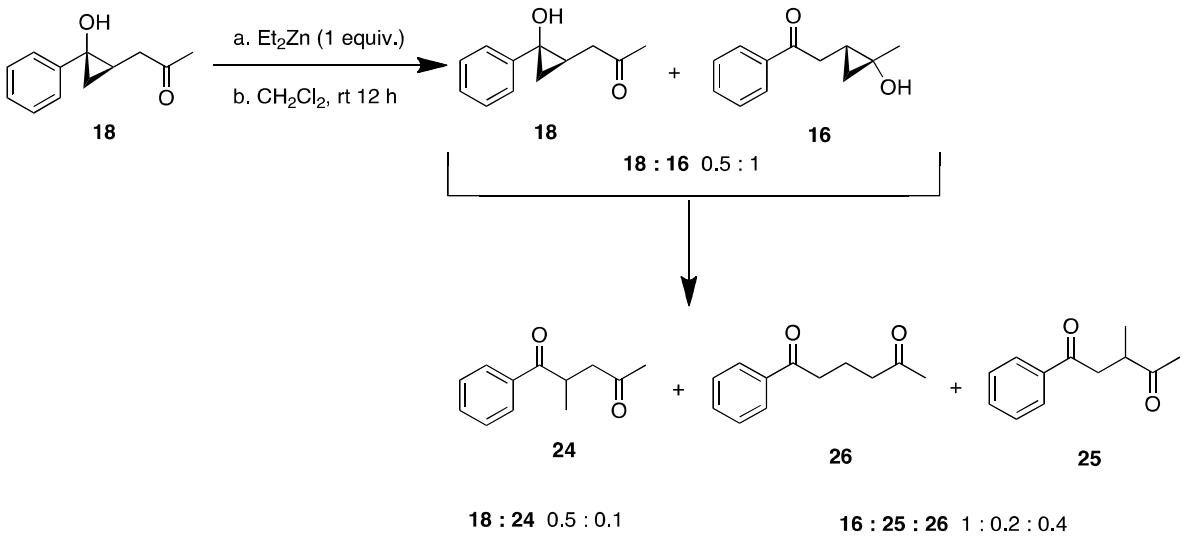
3.1 Zinc-mediated cyclopropanoxide rearrangements:

To confirm the observations of non-cyclopropane containing byproducts made within the homologation-cyclopropanation reaction, the aryl cyclopropanol **18** was isolated from the crude reaction mixture and exposed to diethylzinc (Et_2Zn) in dichloromethane. A one hour reaction resulted in the formation of a 1 : 1 mixture of the regioisomeric cyclopropanols **16** and **18** which provided direct evidence once again, of the rearrangement mechanism (**Scheme 3.1**). It is worth noting that, the one hour diethylzinc rearrangement results in the formation of a 1 : 0.5 mixture of the the aryl cyclopropanol **18** and the β-methyl-γ-diketone **24**. The rearrangement at the same time also resulted in the formation of the chain extended δ-diketone **26** along with the methyl cyclopropanol **16** in a 1 : 0.5 ratio.



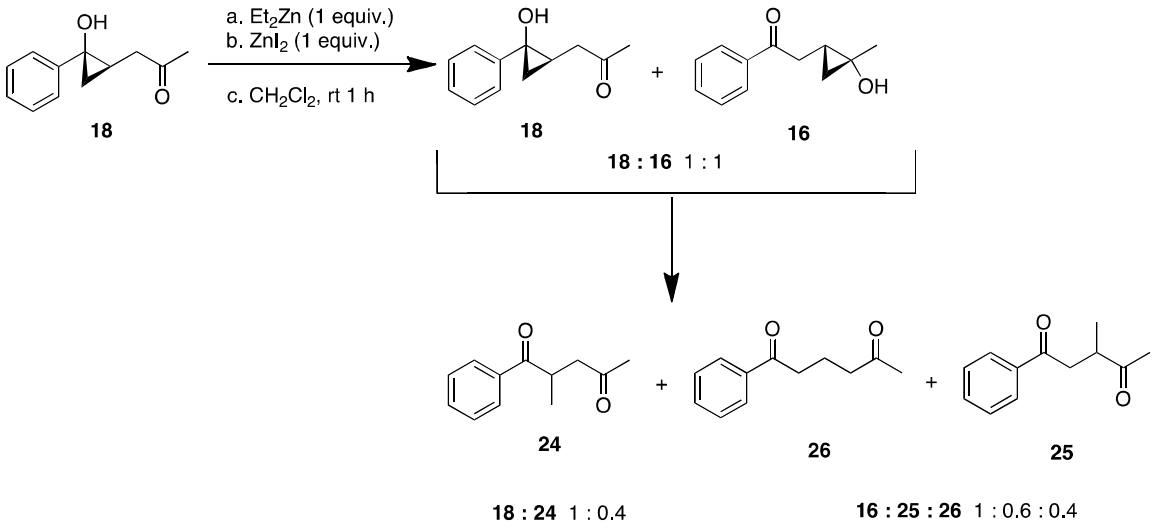
Scheme 3.1: Proposed cyclopropanoxide rearrangement of the aryl cyclopropanol **18** using diethylzinc under reduced reaction times

However after 12 h, the crude reaction mixture revealed the presence of a 1 : 0.5 mixture of the regioisomeric cyclopropanoxides **16** and **18.** The formation of a 1 : 0.2 : 0.4 mixture of the methyl cyclopropanol **16** along with the α-methylated-γ-diketone **25** and the chain extended δ-diketone **26** indicated that homoketonization of the methyl cyclopropanoxide (i.e. *conjugate base of* **16**) was more favored than α-methylation. Formation of 0.5 : 0.1 mixture of the aryl cyclopropanol **18** and the β-methylated-γ-diketone **24** indicated that cyclopropanoxide rearrangement was favored over α-methylation. Formation of minor amounts of α- and β-methylated-γ-diketones **24** and **25**, was believed to result from the ring fragmentation of the regioisomeric cyclopropanoxides (i.e. *conjugate bases of* **18** and **16)** within the crude reaction mixture (**Scheme 3.2**).



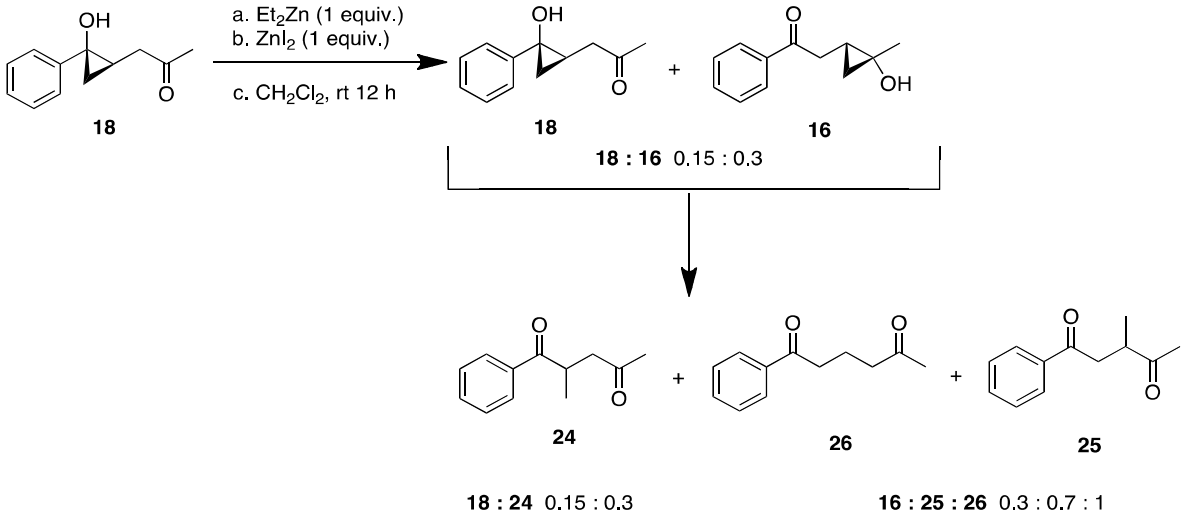
Scheme 3.2: Proposed cyclopropanoxide rearrangement of **18** and ring fragmentation of **16** using diethylzinc for extended time

Accidentally subjecting the aryl cyclopropanol **18** to react with a mixture of diethylzinc and diiodozinc (ZnI_2)[39] for 1 h also resulted in the conversion of the aryl cyclopropanoxide (i.e. *conjugate base of* **18)** to a 1 : 1 mixture of the regioisomeric cyclopropanoxides **18** and **16**. The reaction mixture also revealed the presence of a 1 : 0.4 : 0.6 mixture of the methyl cyclopropanol **16** along with the α-methylated-γ-diketone **25** and the chain extended δ-diketone **26** indicating that α-methylation of **16** was slightly favored over homoketonization under the reaction condtions. Formation of a small amount of β-methylated-γ-diketone **24** resulted from the ring fragmentation of the aryl cyclopropanoxide (*i.e. conjugate base of* **18**) suggested once again that cyclopropanoxide rearrangement of **18** to the methyl cyclopropanoxide (i.e. *conjugate base of* **16**) was more favored over α-methylation of the aryl cyclopropanoxide (i.e. *conjugate base of* **18**) to 24 (**Scheme 3.3**).



Scheme 3.3: Proposed cyclopropanoxide rearrangement of **18** using diethylzinc in presence of diiodozinc (ZnI_2) under reduced reaction times

Analysis of the crude reaction mixture after 12 h revealed the formation of a 1 : 0.7 : 0.3 mixture of the chain extended δ-diketone **26**, the α-methylated-γ-diketone **25** along with the methyl cyclopropanol **16** (**Scheme 3.4**).

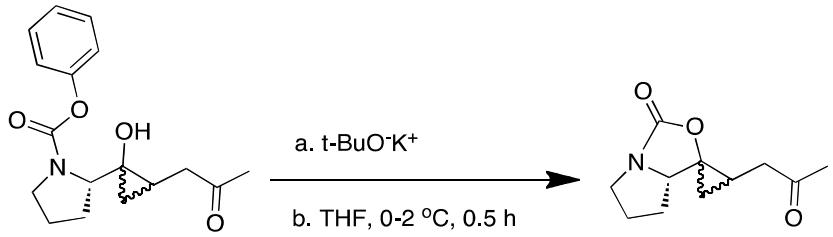


Scheme 3.4: Proposed cyclopropanoxide rearrangement of **18** and ring fragmentation of **16** using diethylzinc in presence of diiodozinc (ZnI_2) for extended time periods

The formation of β-methyl-γ-diketone **24** was suggested to be a result of ring fragmentation of **18** resulting in α-methylation. However formation of 0.7 : 1 mixture of **25** and **26** resulting from the fragmentation of the methyl cyclopropanoxide (i.e. *conjugate base of* **16**) revealed that homoketonization was slightly favored over α-methylation. The results observed within the zinc-mediated cyclopropanoxide rearrangements confirmed the existence of two different mechanistic pathways that are operational during ring fragmentation and that the nature of the zinc reagents (i.e. diethylzinc or diethylzinc + diiodozinc) could affect the reaction mechanism and the rates of ring fragmentation of the regioisomeric cyclopropanols.[39,42]

3.2 Potassium-mediated cyclopropanoxide rearrangements:

Moran[34] and Zercher reported formation of a tricyclic species **37** when phenyl carbamate protected proline cyclopropanols **36** were treated with potassium *tert*-butoxide (t-BuO$^-$K$^+$) (**Scheme 3.5**).

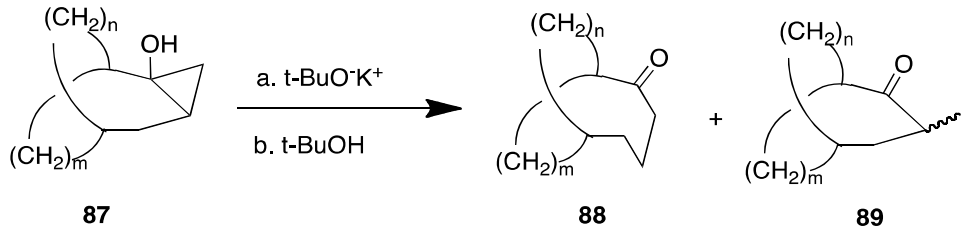


36 **37**

Scheme 3.5: Potassium *tert*-butoxide mediated cyclization of cyclopropanol **36** to tricyclic system **37**

Fragmentation of tertiary cyclopropanols in nortricyclic systems using potassium *tert*-butoxide (t-BuO$^-$K$^+$) is a well-reported reaction and has synthetic utility for ring expansion.[43,49] Hoyano[43] and co-workers reported that potassium *tert*-butoxide (t-BuO$^-$K$^+$) could catalyze both

homoketonization and α-methylation of cyclopropanoxides within nortricyclic systems (**Scheme 3.6**).

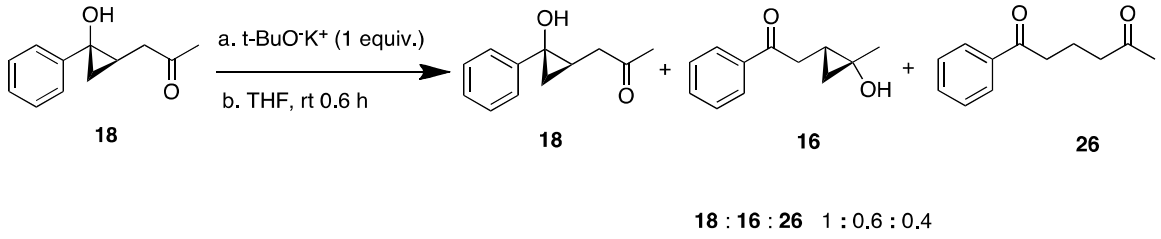


87 **88** **89**

Scheme 3.6: Potassium *tert*-Butoxide (t-BuO$^-$K$^+$) mediated α-methylation and homoketonization of **87**

They reported that room temperature conditions favored homoketonization however, heating to a reflux as well as increase in bridge-size (i.e. n=3 and m=2) favored α-methylation.

Based on this idea, the aryl cyclopropanol **18** was subjected to react with stoichiometric amounts of potassium *tert*-butoxide (t-BuO$^-$K$^+$) in tetrahydrofuran (THF). The reaction was monitored by thin layer chromatography (TLC) at various times until 12 h, at which time the reaction was quenched. Individual aliquots of the crude reaction mixture were collected at specific reaction times and analyzed using NMR spectroscopy (**Scheme 3.7**). After 1 h of the reaction time, the aryl cyclopropanoxide **18** yielded a 1 : 0.6 : 0.4 mixture of the regioisomeric cyclopropanols **18** and **16** along with the chain extended δ-diketone **26**.

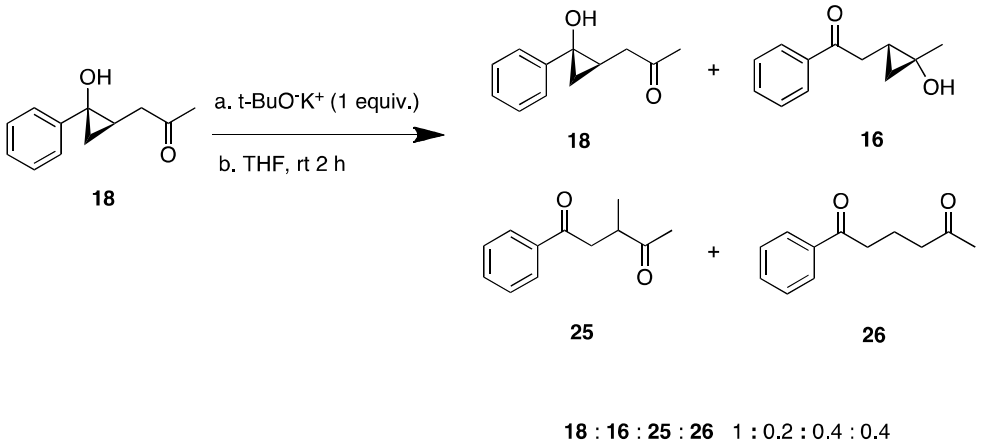


18 **18** **16** **26**

18 : **16** : **26** 1 : 0.6 : 0.4

Scheme 3.7: Proposed cyclopropanoxide rearrangement of aryl cyclopropanol **18** using potassium *tert*-butoxide

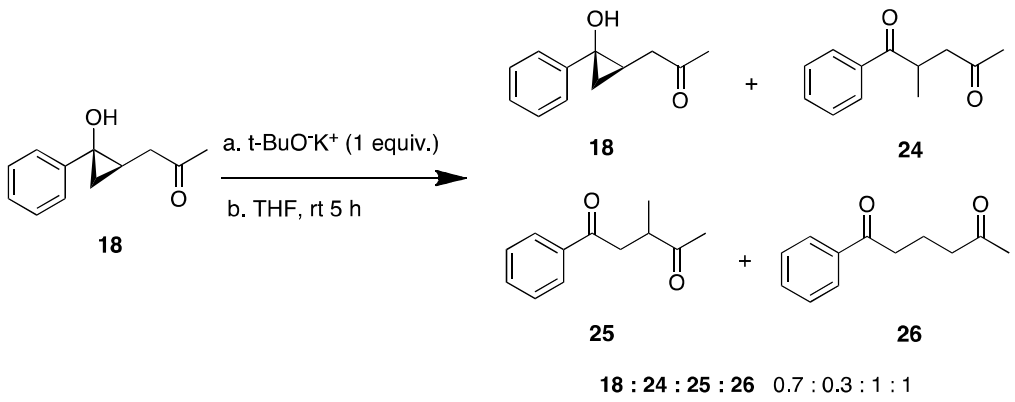
However after 2 h, the crude reaction mixture revealed the presence of the regioisomeric cyclopropanols **18** and **16** along with the α-methylated-γ-diketone **25** and the chain extended δ-diketone **26** in a 1 : 0.2 : 0.4 : 0.4 ratio (**Scheme 3.8**).



Scheme 3.8: Proposed cyclopropanoxide rearrangement of **18** and ring fragmentation of **16** to **25** and **26** using potassium *tert*-butoxide

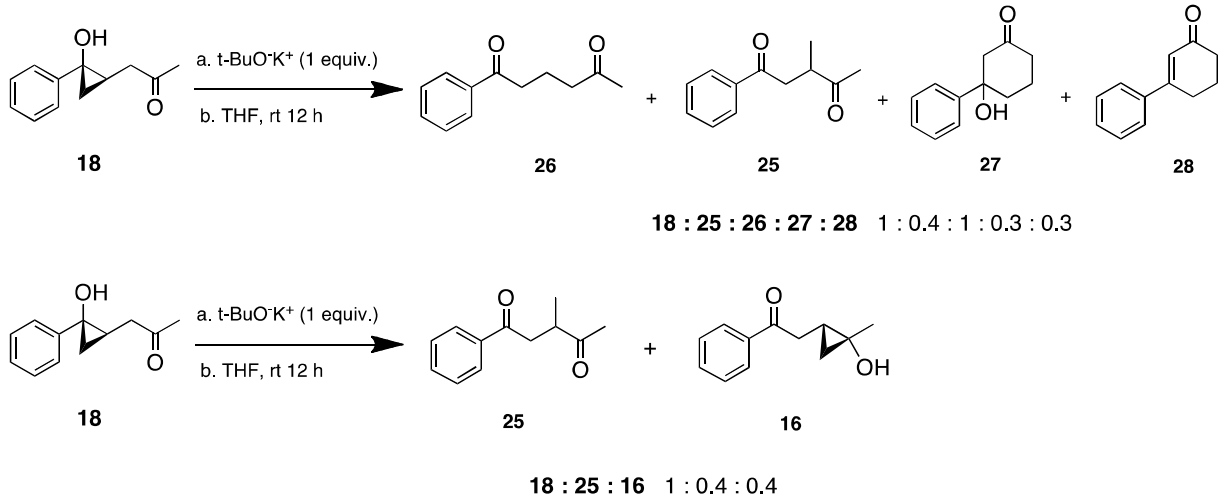
The formation of a 1 : 1 mixture of **25** and **26** was indicative of two ring fragmentation pathways resulting from the methyl cyclopropanoxide (i.e. *conjugate base of* **16**).

Analysis of the crude reaction mixture after 5 h revealed the presence of a 1 : 1 : 1 mixture of the aryl cyclopropanol **18** along with α-methylated-γ-diketone **25** and the chain extended δ-diketone **26** (**Scheme 3.9**). A minor amount of the β-methylated-γ-diketone obtained through the ring fragmentation of the aryl cyclopropanoxide (i.e. *conjugate base of* **18**) was forming in an equimolar amount with the methyl cyclopropanoxide (i.e. *conjugate base of* **16**) within the crude reaction mixture. This suggested that ring fragmentation of the methyl cyclopropanoxide (i.e. *conjugate base of* **16**) to **25** was much faster than the ring fragmentation of the aryl cyclopropanoxide (i.e. *conjugate base of* **18**).



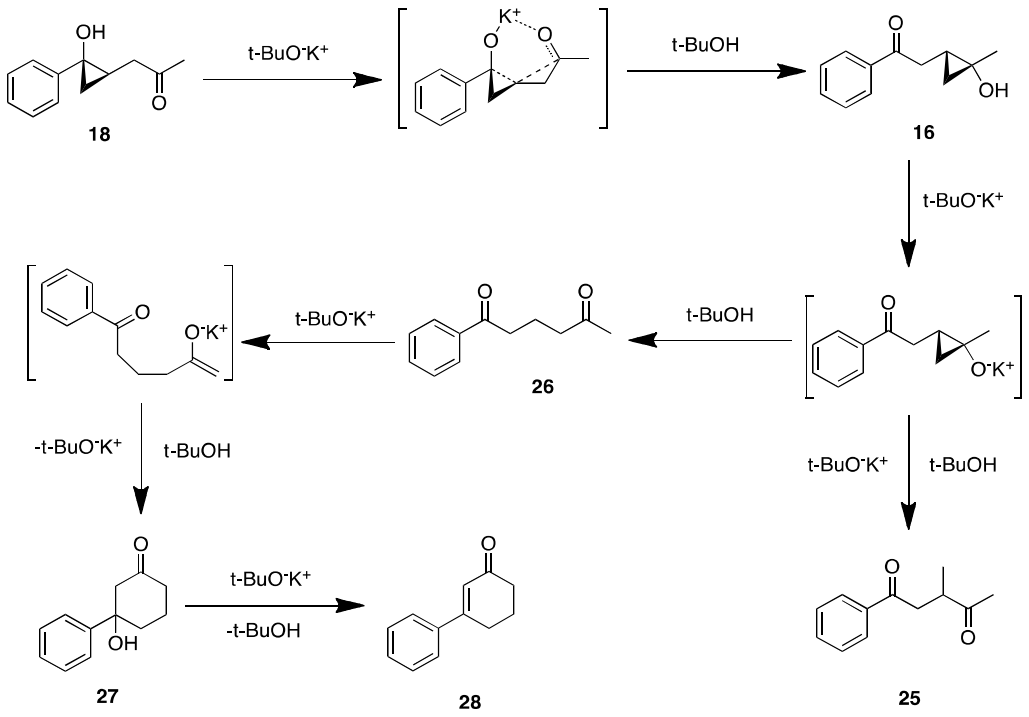
Scheme 3.9: Proposed cyclopropanoxide rearrangement of **18** for 5 h and formation of ring fragmented products **25** and **26** using potassium *tert*-butoxide

The 12 h crude reaction mixture revealed the formation of a mixture of the chain-extended δ-diketone **26** and the α-methylated-γ-diketone **25** in a 1 : 0.4 ratio along minor amounts of 3-hydroxy-3-methyl-cyclohexanone **27** (*ketol*) and 3-methyl-2-cyclohexen-1-one **28** (*enone*) respectively. It is also worth noting that the crude reaction mixture also revealed the presence of a 0.4 : 0.4 mixture of **25** and the methyl cyclopropanol (i.e. *conjugate base of* **16**) [**Scheme 3.10**]



Scheme 3.10: cyclopropanoxide rearangement of **18** to **16** and formation of the *ketol* **27** and the *enone* **28** using potassium tert-butoxide

The proposed mechanism for t-BuO$^-$K$^+$ mediated cyclopropanoxide rearrangement is illustrated below (**Scheme 3.11**).[22]



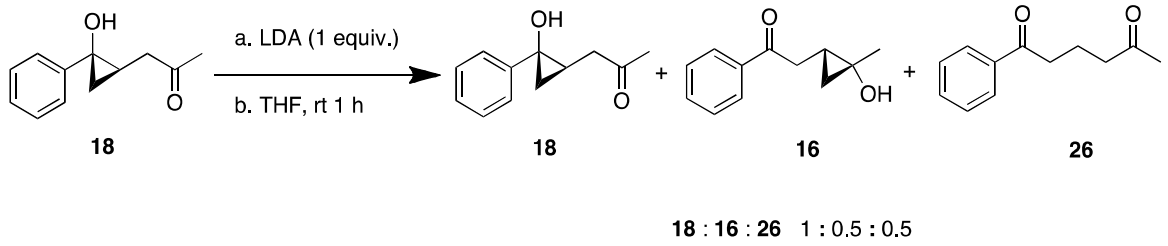
Scheme 3.11: Proposed mechanism for t-BuO$^-$K$^+$ - mediated cyclopropanoxide rarrangement

The *enone* **28** within the crude reaction mixture was believed to result from an intramolecular aldol condensation **26** followed by a β-elimination.

3.3 Lithium-mediated cyclopropanoxide rearrangements:

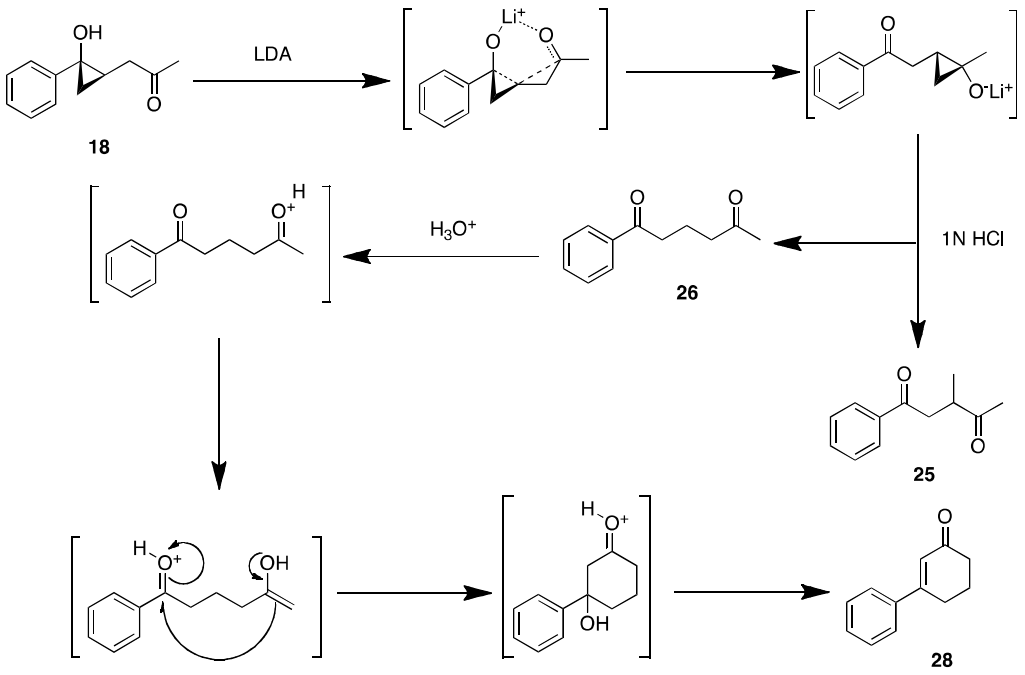
Sterically encumbered amines like lithium diisopropyl amide (LDA) was also employed to investigate cyclopropanoxide rearrangements using the aryl cyclopropanol **18**. The investigation was initially carried out using LDA in tetrahydrofuran (THF). The LDA was generated *in-situ* prior to the addition of the aryl cyclopropanol **18**. The solution was sampled after 1 h and again after an overnight stir of 12 h. Individual aliquots of the crude reaction mixture were isolated and analyzed using NMR spectroscopy for both durations. The analyzed results for the 1 h reaction

displayed the presence of a 1 : 0.5 : 0.5 mixture of the regioisomeric cyclopropanoxides **18** and **16** along the chain extended δ-diketone **26 (Scheme 3.12).**



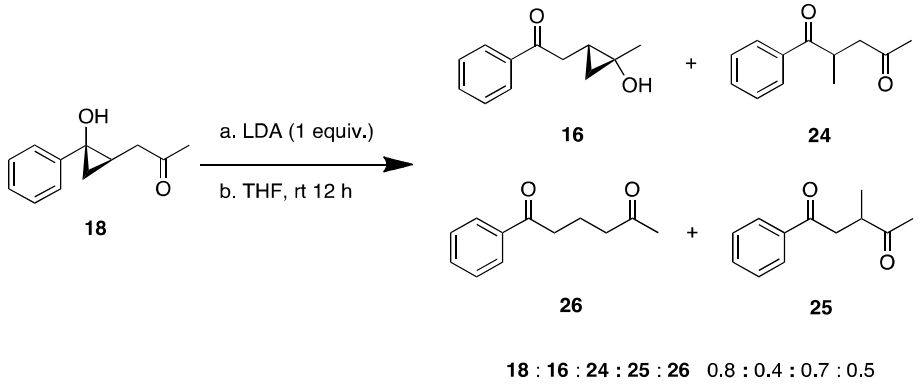
Scheme 3.12: Proposed LDA-mediated cyclopropanoxide rearrangement of **18** followed by homoketonization of **16**

The crude reaction mixture however was inadvertently worked up using 1N hydrochloric acid (HCl), and extracted after sitting in acid for 12 h. The NMR analysis of the 12 h crude reaction mixture surprisingly exhibited the presence of 3-methyl-2-cyclohexen-1-one **28** (*enone*) along with a small amount of the β-methyl-γ-diketone **24**. The formation of 3-hydroxy-3-methyl-cyclohexanone **15** (*ketol*) was, however, not observed. Formation of the *enone* **28** was attributed towards the acid-catalyzed intramolecular aldol reaction of the chain-extended δ-diketone **26** followed by elimination (**Scheme 3.13**).



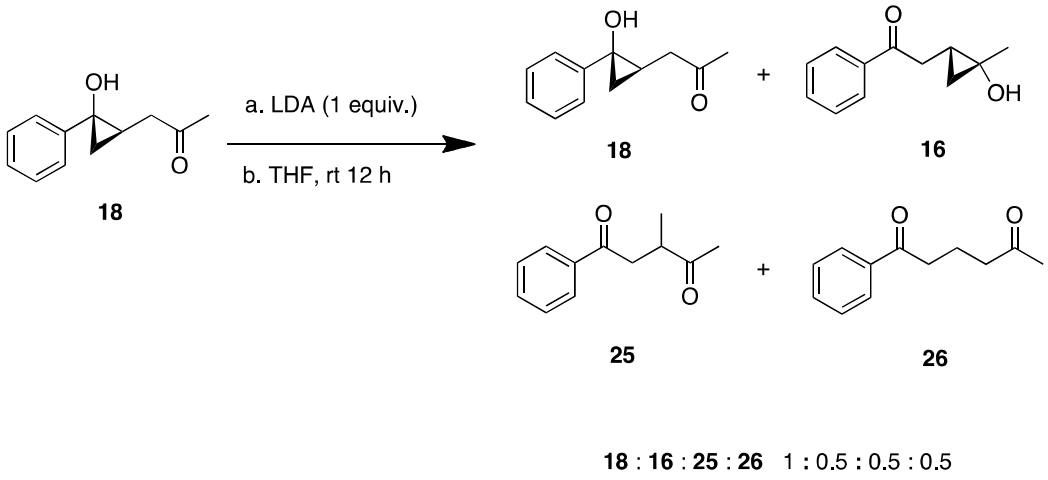
Scheme 3.13: Proposed mechanism for LDA-mediated cyclopropanoxide rearrangement of **18**

Formation of the α-methylated-γ-diketone **25** and the chain extended δ-diketone **26** in the 12 h reaction mixture once again was consistent the acid-catalysed ring fragmentation of the methyl cyclopropanol **16** using catalytic amounts of *p*-toluenesulfonic acid (*p*-TsOH) as described earlier by Li[38] and co-workers (**Scheme 3.14**).



Scheme 3.14: LDA-mediated cyclopropanoxide rearrangement of **18** in the presence of 1N hydrochloric acid

Repeating the experiment for 12 h and working up the crude reaction mixture with a mild acid (e.g. aqueous ammonium chloride) revealed the presence of a 1 : 0.5 : 0.5 : 0.5 mixture of the regioisomeric cyclopropanols **18** and **16**, the α-methylated-γ-diketone **25** and the chain extended δ-diketone **26** respectively (**Scheme 3.15**).



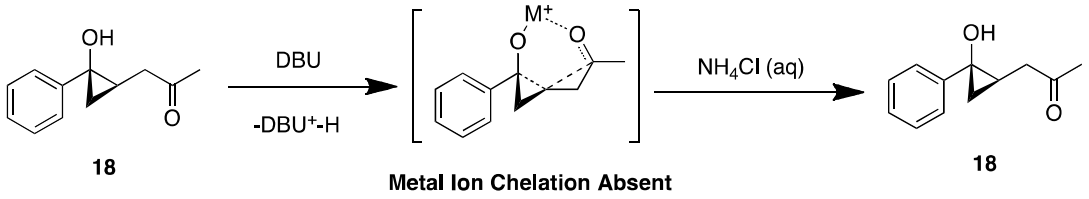
Scheme 3.15: Proposed LDA-mediated cyclopropanoxide rearrangement of **18** and ring fragmentation of **16** under extended time periods

The formation of **25** and **26** in approximately 1 : 1 ratio once again confirmed that the two fragmentation pathways were operating for the regioisomeric cyclopropanoxide (i.e. *conjugate base of* **16**). Formation of trace amounts of enone **28** and the β-methyl-γ-diketone **24** was also noticed within the crude reaction mixture.

3.4 Cyclopropanoxide rearrangements mediated by sterically encumbered non-ionic bases:

Subjecting the aryl cyclopropanol **18** to neutral amine bases in dichloromethane (DCM) for 5 h resulted in no rearrangement or fragmentation. Only the unreacted starting material was observed in the crude reaction mixture (i.e. aryl cyclopropanol **18**). The reaction was performed

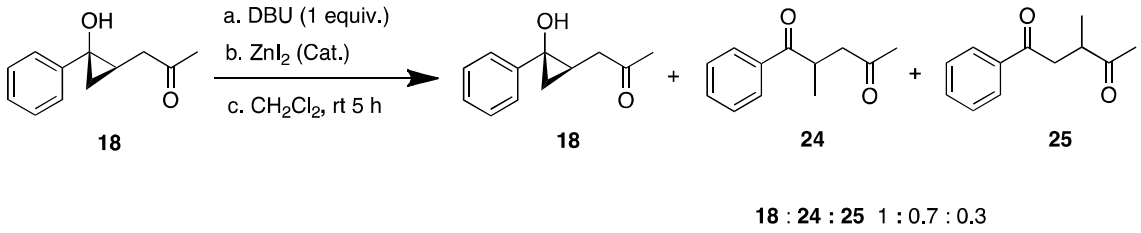
with a variety of bases, including DBU, triethylamine, diisopropyl amine and *N*-diisopropylethylamine. No rearrangement or fragmentation was observed under the reaction conditions (**Scheme 3.16**).



Scheme 3.16: Proposed DBU mediated rearrangement of the aryl cyclopropanoxide **18**

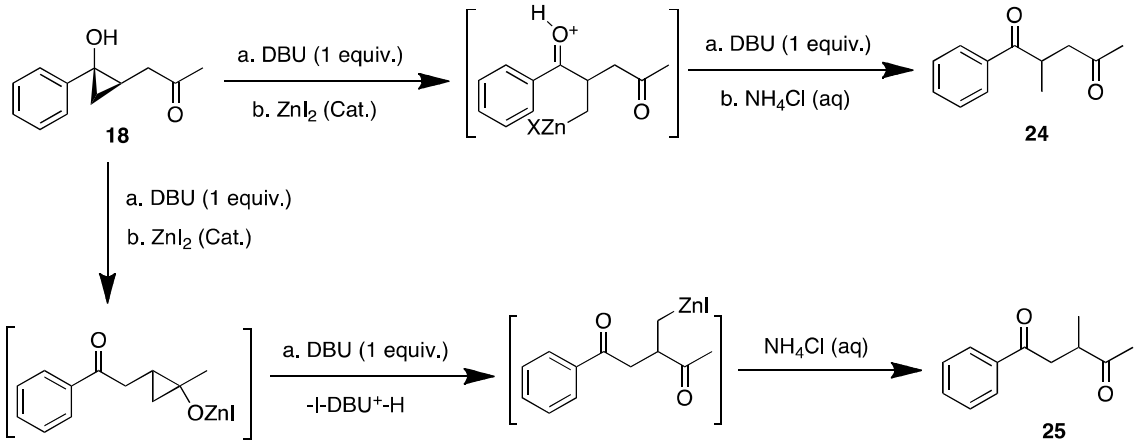
This observation was attributed mainly due to two reasons: (a). Inability to form the cyclopropanoxide (i.e. conjugate base of **18**) with these relatively weak bases and the absence of any metal ion chelation to facilitate the rearrangement.

The reaction was performed one more time by subjecting the aryl cyclopropanol **18** to DBU in dichloromethane (DCM). The reaction was monitored by both TLC and NMR analysis over a period of 5 h. The presence of unreacted aryl cyclopropanol **18** within the 5 h crude reaction mixture indicated that no cyclopropanoxide rearrangements were occurring during the reaction; however addition of a catalytic amount of diiodozinc (ZnI_2) to the reaction mixture resulted in the formation of a 1 : 1 mixture of β-methyl-γ-diketone **24** and the aryl cyclopropanol **18** within an additional 4 h. Formation of minor amounts of **25** within the crude reaction mixture revealed a rapid cyclopropanoxide rearrangement followed by ring fragmentation of the methyl cyclopropanoxide (i.e. *conjugate base of* **16**) (**Scheme 3.17**).



Scheme 3.17: Proposed cyclopropanoxide rearrangement of aryl cyclopropanol **18** using DBU in presence of diiodozinc

These mechanism illustrated below (**Scheme 3.18**) describes the sequence of events resulting in cyclopropanoxide rearrangements followed by two alternate modes of ring fragmentation. However the preferred mode results in the formation of α- and β-methylated-γ-diketones **24** and **25** as opposed to the chain extended δ-diketone **26** (product not shown).

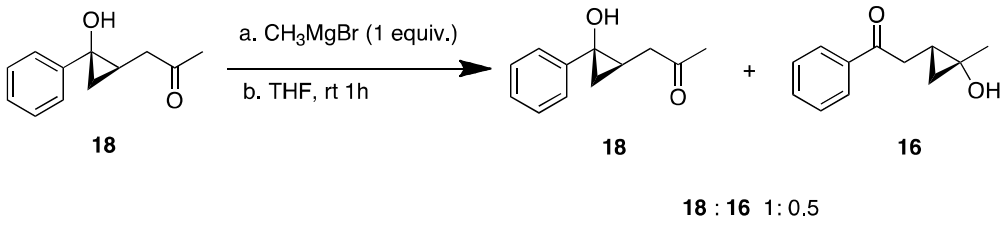


Scheme 3.18: Proposed mechanism for cyclopropanoxide rearrangement of **18** followed by α-methylation of **16**

3.5 Magnesium-mediated cyclopropanoxide rearrangements:

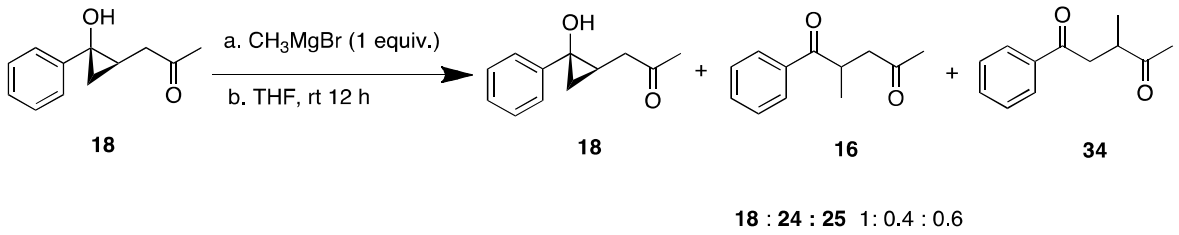
The use of diethylzinc to facilitate cyclopropanoxide rearrangements is already described earlier in chapter-2. The use of alternate organometallic compounds to facilitate the rearrangement of **18** was investigated. A stoichiometric amount of methyl magnesium bromide

(CH_3MgBr) (1.0 M in diethyl ether) was added to **18** in tetrahydrofuran (THF). The reaction was monitored by TLC over a period of 12 h. An aliquot was removed after 1 h and the crude mixture was analyzed using by NMR. A 1 : 0.5 mixture of the regioisomeric cyclopropanols **18** and **16** were identified (**Scheme 3.19**).



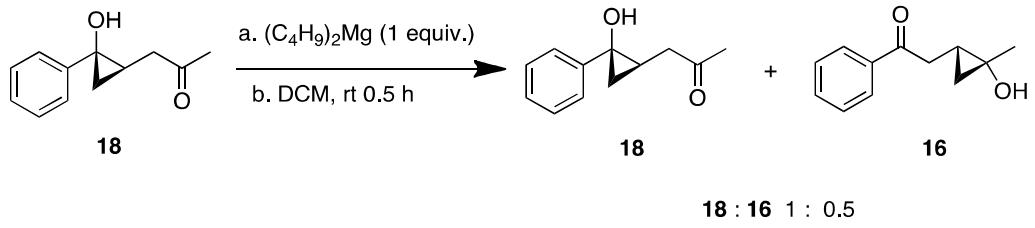
Scheme 3.19: Proposed cyclopropanoxide rearrangement of aryl cyclopropanol **18** using a methyl Grignard

However NMR analysis of the 12 h crude reaction mixture revealed the presence of a 1 : 0.6 : 0.4 mixture of the aryl cyclopropanol **18** and the α- and β-methylated-γ-diketones **24** and **25** (**Scheme 3.20**).



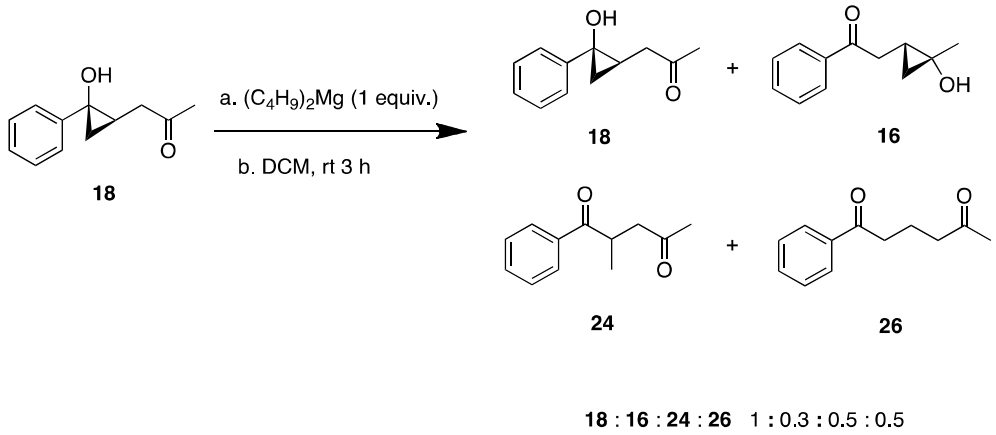
Scheme 3.20: Methyl Grignard mediated cyclopropanoxide rearrangement of **18** under extended reaction times.

Exposure of **18** to stoichiometric amounts of di-n-butyl magnesium (1.0 M in heptane) [$(C_4H_9)_2Mg$] in dichloromethane (DCM) for 0.5 h resulted in the formation of a 1 : 0.5 mixture of the regioisomeric cyclopropanoxides (i.e. conjugate bases of **18** and **16**) (**Scheme 3.21**).



Scheme 3.21: Proposed cycloproanoxide rearrangement of aryl cyclopropanol **18** using di-n-butylmagnesium

When the reaction was allowed to proceed for 3 h, formation of a 0.5 : 0.5 mixture of the chain extended δ-diketone **26** and the β-methyl-γ-diketone **24** was observed along with the regioisomeric cyclopropanols **18** and **16** (1 : 0.3). The results were determined by NMR spectroscopy of the crude reaction mixture after work-up (**Scheme 3.22**).

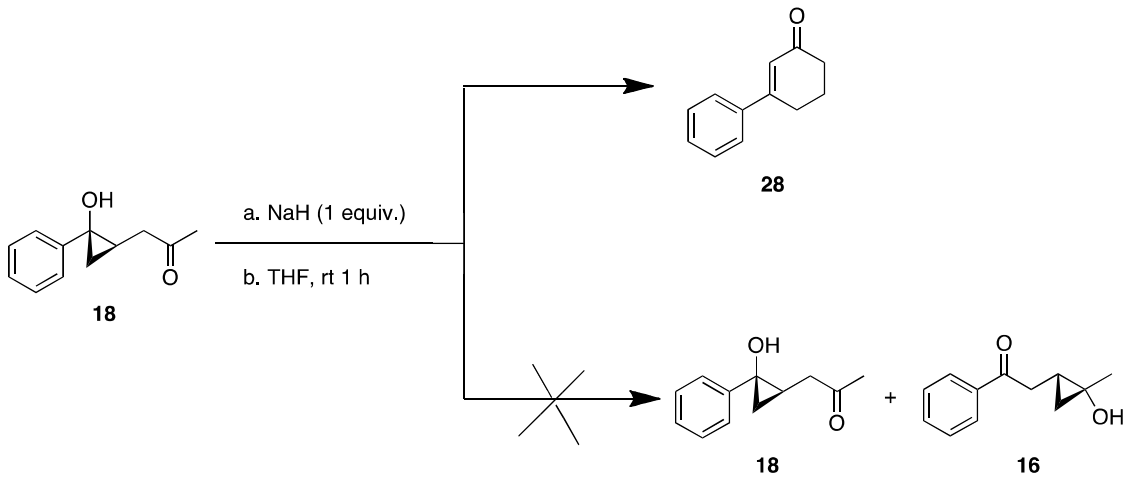


Scheme 3.22: Proposed di-n-butylmagnesium rearrangement of **18** and ring fragmentation of **18** and **16** to **24** and **26**

3.6 Sodium-mediated cyclopropanoxide rearrangements:

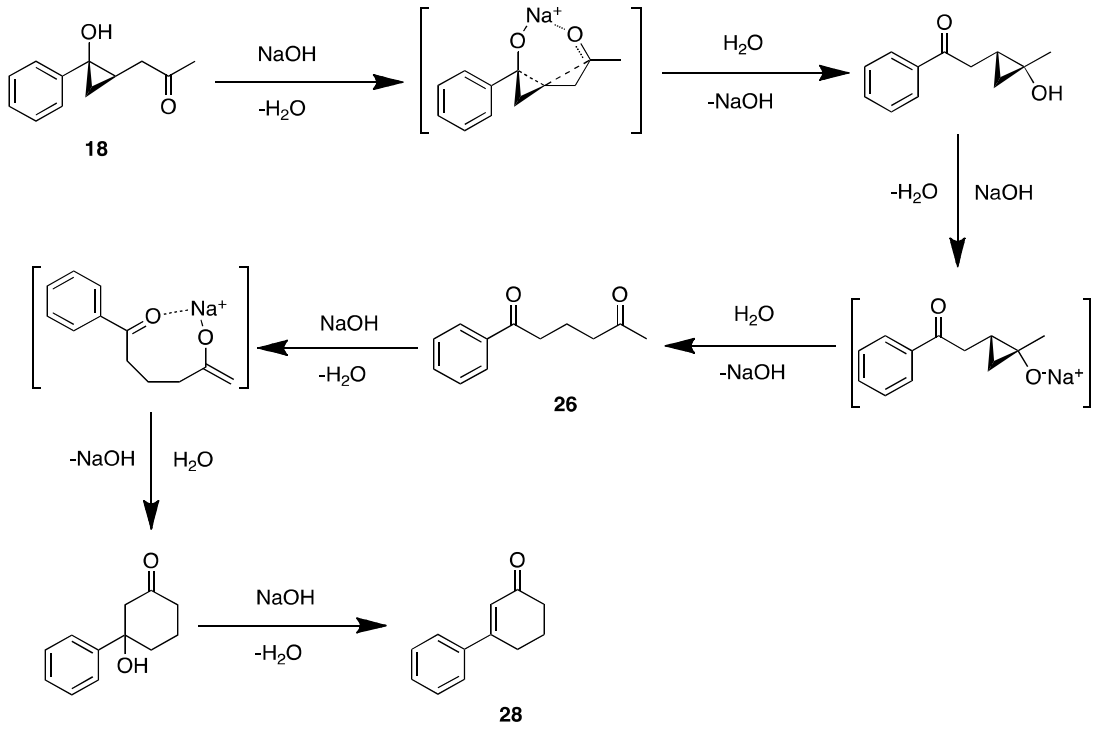
Following the seminal work of Nickon[41] and co-workers, the use of metal hydrides for initiating cyclopropanoxide rearrangements was also investigated. Aryl cyclopropanol **18** was subjected to a stoichiometric amount of sodium hydride (NaH) [60% dispersion in mineral oil] in

tetrahydrofuran (THF) for 1 h. The reaction mixture was worked up and extracted to isolate the crude reaction mixture, which was then analyzed using NMR spectroscopy. The analysis of the crude reaction mixture indicated the unexpected formation of the *enone* **28** rather than a mixture of regioisomeric cyclopropanols **18** and **16** (**Scheme 3.23**). This observation was attributed towards sodium hydride (NaH) being either contaminated with sodium hydroxide or being converted to sodium hydroxide (NaOH) through exposure to moisture in the solvent THF.



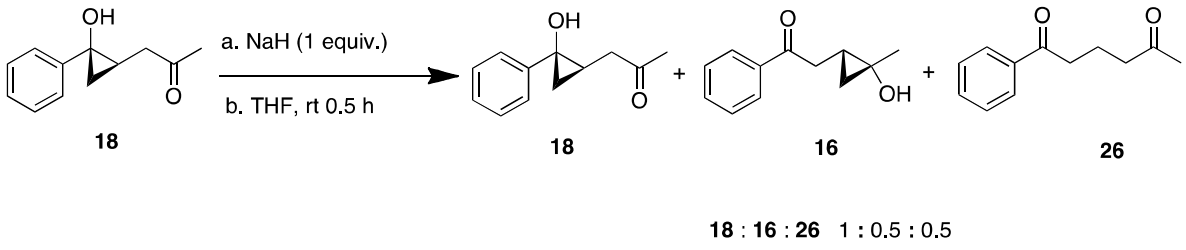
Scheme 3.23: Initial results for proposed sodium hydride-mediated cyclopropanoxide rearrangements of the aryl cyclopropanol **18**

The presence of sodium hydroxide could promote the conversion of **18** to the methyl cyclopropanoxide (i.e. conjugate base of **16**). Ring fragmentation of the methyl cyclopropanoxide **16** (i.e. *homoketonization*) could have resulted in the preferential formation of the chain extended δ-diketone **26**, which under basic conditions could participate in an aldol reaction followed by elimination to form **28** (**Scheme 3.24**).[50] Similar observations for chain extended diketones undergoing aldol condensation using sodium hydroxide (NaOH) was reported by Li and co-workers,[38] however formation of the conjugated *enone* **28** was not reported.



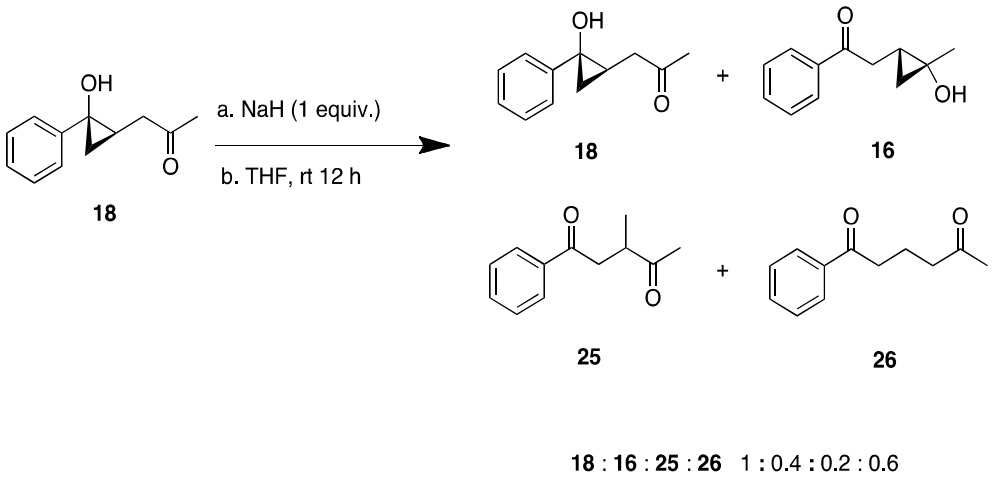
Scheme 3.24: Proposed mechanism for cyclopropanoxide rearrangement of aryl cyclopropanol **18** and unexpected formation of the *enone* **28**

Repeating the experiment with anhydrous tetrahydrofuran (THF) and sampling the reaction after 1 h revealed the conversion of aryl cyclopropanol **18** to a 1 : 0.5 : 0.5 mixture of the regioisomeric cyclopropanols **18** and **16** along with the chain-extended δ-diketone **26** (**Scheme 3.25**).



Scheme 3.25: Proposed cyclopropanoxide rearrangement of the aryl cyclopropanol **18** and ring fragmentation to **26** using sodium hydride

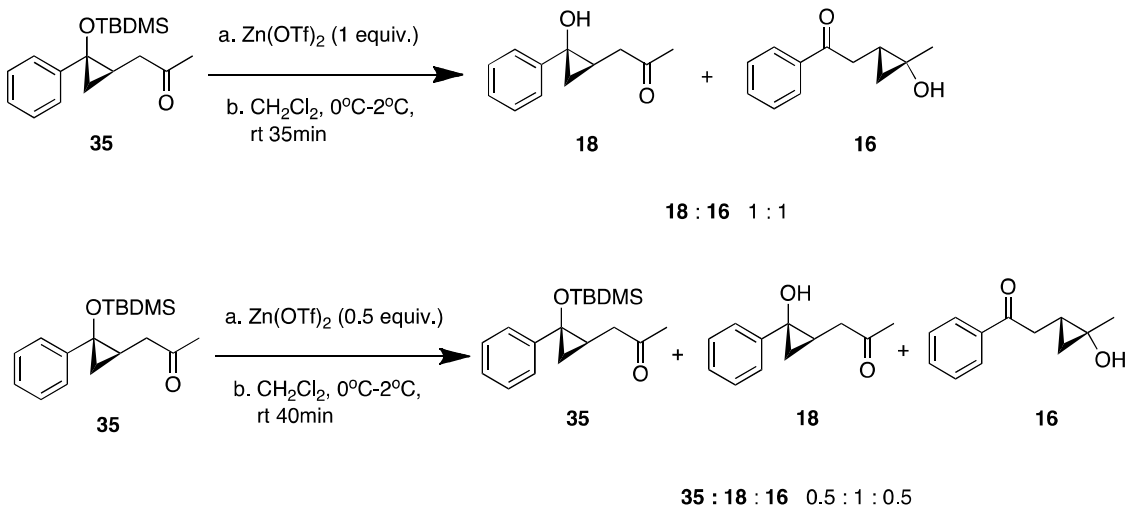
The reaction mixture quenched and worked up after 12 h. NMR analysis of the crude reaction mixture revealed the presence of a 1 : 0.4 : 0.2 : 0.6 ratio of the regioisomeric cyclopropanols **18** and **16** along with the α-methylated-γ-diketone **25** and the chain extended δ-diketone **26** (**Scheme 3.26**). A trace amount of β-methylated-γ-diketone **24** within the crude reaction mixture was believed to result from the direct ring fragmentation of the aryl cyclopropanoxide (i.e. conjugate base of **18**).



Scheme 3.26: Proposed NaH mediated cyclopropanoxide rearrangements of **18** followed by ring fragmentation of **16** to **25** and **26** under extended time periods

3.7 *Tert*-butyldimethylsilyl (TBDMS) deprotection and cyclopropanoxide rearrangement:

The involvement of metal ion chelation during cyclopropanoxide rearrangements was also probed by preparing the *tert*-butyldimethylsilyl (TBDMS) ether of the aryl cyclopropanol **18** and subjecting it to zinc triflate [$Zn(OTf)_2$].[51-53] The reaction was executed once with sub-stoichiometric and once with stoichiometric amounts of the anhydrous Lewis acid, and both reactions were monitored for approximately 40 min (**Scheme 3.27**).

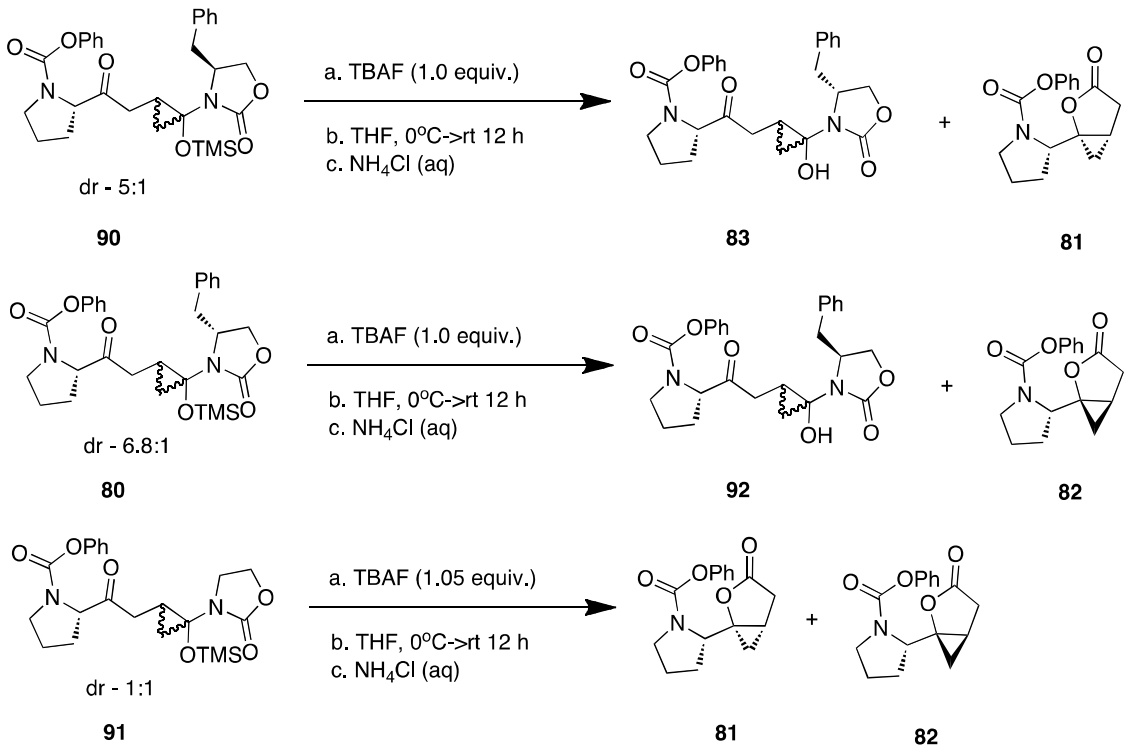


Scheme 3.27: Proposed zinc triflate-mediated TBDMS deprotection of **35** followed by cyclopropanoxide rearrangement

Use of 0.5 equivalents (5 mole percent) of zinc triflate resulted in the formation of the regioisomeric cyclopropanols **18** and **16** in a 1 : 0.5 ratio along with the unreacted TBDMS starting material **35**. However use of 1.1 equivalents (10 mole percent) of zinc triflate resulted in complete deprotection of the TBDMS ether **35** and generation of the regioisomeric cyclopropanoxides **18** and **16** in a 1 : 1 ratio.

In studies of systems that were derived from β-keto imides, Zercher group members have reported the formation of bicyclic lactones that resulted from a cyclopropanoxide rearrangement involving metal-ion chelation (i.e. use of zinc counter-ion).[26,34,35] However Bhogadhi[58] and Zercher investigated that TBAF-mediated deprotection of TMS-protected cyclopropyl ethers could initiate similar rearrangements in the absence of metal-ion chelation (i.e. without using the zinc-carbenoid). Bhogadhi reported that TBAF-mediated rearrangement of TMS-protected cyclopropanols **90** and **80** resulted in the formation of the bicyclic lactones **81** (**S, S** isomer) and **82** (**R, S** isomer) as a single diastereomer along with trace amounts of cyclopropanols **83** and **92**.

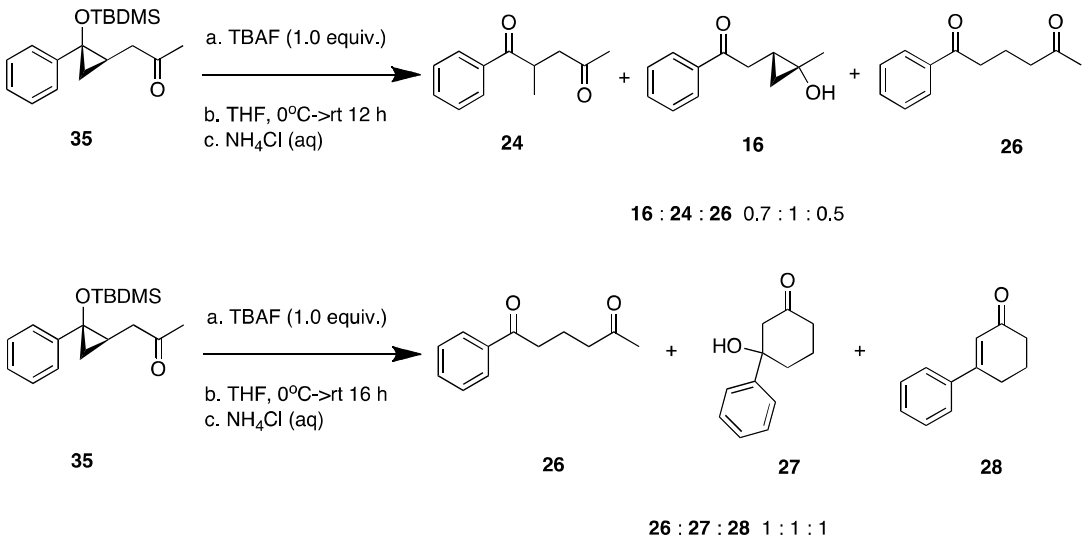
However, TBAF-mediated rearrangement of the TMS-protected cyclopropanol **91** resulted in the formation of a diastereomeric mixture bicyclic lactones **81** and **82** (**Scheme 3.28**).



Scheme 3.28: TBAF mediated deprotection of TMS-protected cyclopropanols **80, 90** and **91**

The results obtained above encouraged the treatment of the silyl ether **35** with TBAF. The reaction was monitored by thin layer chromatography over a period of 16 h at which time the reaction was quenched. Individual aliquots of the crude reaction mixture were collected at a number of time intervals, worked up and analyzed using NMR spectroscopy. The NMR analysis of the crude reaction mixture after 12 h revealed the presence of the methyl cyclopropanol **16**, the β-methylated-γ-diketone **24** and the chain extended δ-diketone **26** indicating that rearrangement of the cyclopropanoxides was occurring, as well as ring fragmentation to provide **24** and **26**. However NMR analysis of the crude reaction mixture obtained after 16 h mainly

revealed the presence of the chain extended δ-diketone **26**, 3-hydroxy-3-methyl-cyclohexanone **27** (*ketol*) and 3-methyl-2-cyclohexen-1-one **28** (*enone*) [**Scheme 3.29**]

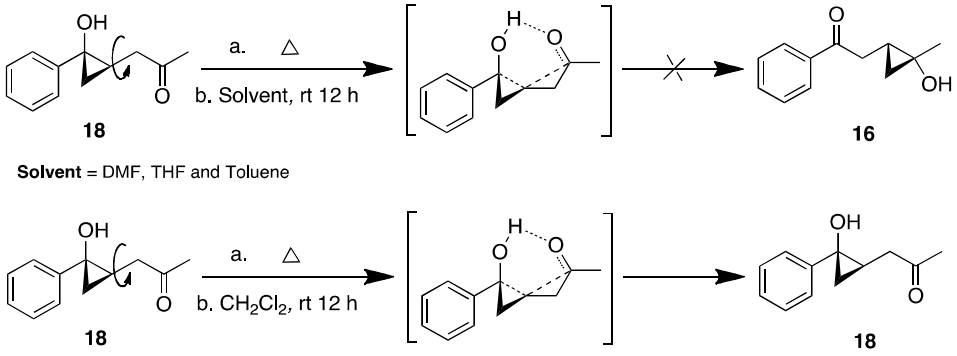


Scheme 3.29: TBAF mediated rearrangement of TBDMS-protected cyclopropanol **35**

3.8 Thermal rearrangements:

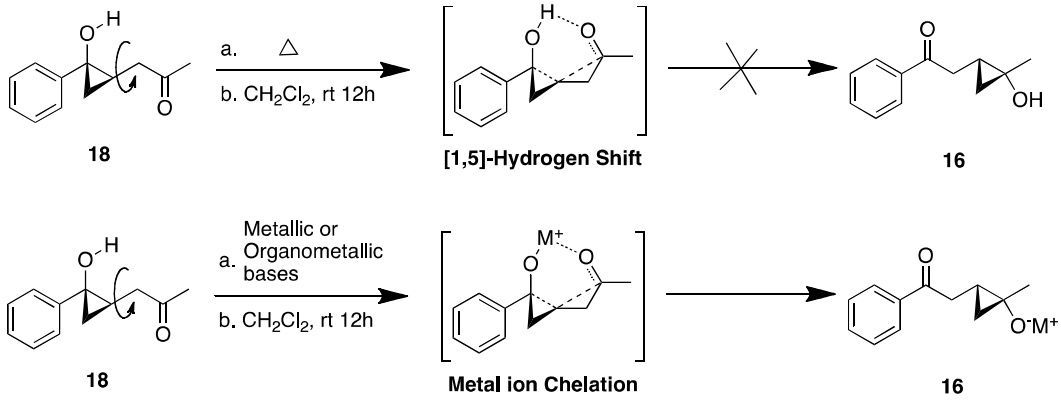
As described earlier in **Scheme 1.6**, Taschner's observed a rearrangement that could be rationalized as involving a *sigmatropic rearrangement* of the silyl ether during a TMSCl mediated homologation-cyclopropanation reaction.[26] This led us to rationalize that rearrangements of the aryl cyclopropanol **18** could result in the formation of the methyl cyclopropanol **16** through a [1,5]-hydrogen shift. Up to this point, all investigations reported within this study have utilized the conjugate base of the aryl cyclopropanol **18** in the rearrangement. A study of the rearrangement potential for the parent cyclopropanol was proposed, which would be, in effect, a sigmatropic rearrangement. To confirm this hypothesis the aryl cyclopropanol **18** was dissolved in different high boiling solvents like N,N-dimethylformamide (DMF), toluene and tetrahydrofuran (THF) and subjected to reflux for a period of 12 h. However NMR analysis of the crude reaction mixture after 12 h indicated that the

starting material **18** was decomposed and the targeted product **16** was never observed. The reaction was then performed using a low boiling solvent like dichloromethane (DCM) and monitored periodically by TLC, which indicated no change in reaction constitutents. NMR analysis of the crude reaction mixture, which was worked up after 12 h, likewise indicated only the presence of the starting material rather than a mixture of rearranged cyclopropanols **18** and **16 (Scheme 3.30)**.



Scheme 3.30: Proposed thermal rearrangement of the aryl cyclopropanol **18**

The results obtained above illustrated that direct interconversion of the γ-keto cyclopropanols (**18** to **16**) necessitated the involvement of a *cyclopropanoxide* during the rearrangement (**Scheme 3.31**).



Scheme 3.31: Proposed thermal and base-mediated rearrangement of the aryl cyclopropanol **18**

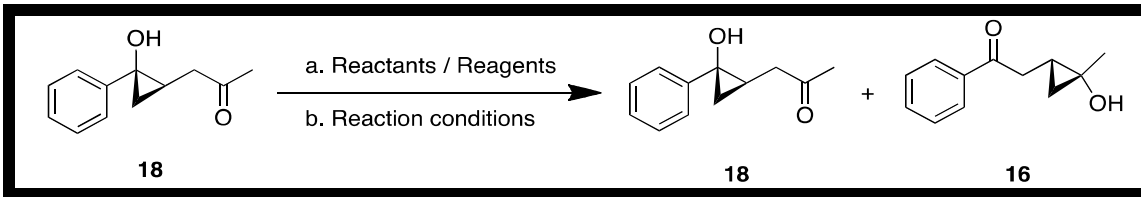
3.9 Results and Discussion:

Cyclopropanoxide fragmentations have been studied and reported by several research groups.[7,40,46,47] The synthetic utility of base-mediated cyclopropanoxide rearrangements has found applications within the Krebs cycle through the rearrangement of methyl malonyl coenzyme A to succinyl coenzyme A using Vitamin B_{12} (i.e. *Cobalamin*) as the cofactor[54]. Successful applications within the Zercher group include: homoketonization followed by ring expansion of γ-keto cyclopropanols[7] and stereoselective formation of tricyclic systems,[34] as well as lactones.[26,33,34,35]

Cyclopropanoxide rearrangements of the aryl cyclopropanol **18** to a 1 : 1 mixture of the cyclopropanoxides (i.e. conjugate bases of **18** and **16**) using a carbenoid species like bis(iodomethyl)zinc [$Zn(CH_2I)_2$] has been reported within the Zercher group. Mower previously reported a time-dependent distribution of the regioisomeric cyclopropanoxides (i.e. *conjugates bases of* **18** and **16**) by identifying the increased formation of the aryl cyclopropanol **18** under reduced reaction times and its rearrangement to the methyl cyclopropanol **16** under extended reaction times (*as described earlier* in **Scheme 1.17**). However, no attempt was made to identify the rearrangement of methyl cyclopropanoxide (i.e. *conjugate base of* **16**) to the aryl cyclopropanoxide (i.e. *conjugate base of* **18**) due to the anticipated difficulty in observing equilibration of the methyl cyclopropanoxide to the aryl cyclopropanoxide owing to disruption of conjugation.

In this thesis counterions other than zinc have been shown to facilitate the cyclopropanoxide rearrangement using the reaction conditions listed down in the table **Table 3**.

Table 3: Cyclopropanoxide rearrangements under the influence of different counter ions for reduced reaction times



18 18 16

Entry	Reagents / Equivalents	Reaction Conditions	#Ratio of (18)	#Ratio of (16)
1.	Diethylzinc (Et_2Zn) / (Et_2Zn/ZnI_2) (1 equiv.)	Dichloromethane (DCM), rt, 1 h	1	1
2.	Sodium hydride (NaH) / (1 equiv.)	Tetrahydrofuran (THF), rt, 0.5 h	1	0.5
3.	Potassium *tert*-butoxide ($t\text{-}BuO^-K^+$) / (1 equiv.)	Tetrahydrofuran (THF), rt, 0.6 h	1.0	0.6
4.	Methylmagnesium bromide (CH_3MgBr) / (1 equiv.)	Tetrahydrofuran (THF), rt, 1 h	1.0	0.5
4.	Di-n-butylmagnesium [$(C_4H_9)_2Mg$] / (1 equiv.)	Dichloromethane (DCM), rt, 0.5 h	1.0	0.5
5.	Lithium diisopropylamide (LDA) / (1 equiv.)	Tetrahydrofuran (THF), rt, 1 h	1.0	0.5
6.	1,8-Diazabicyclo [5.4.0] undec-7-ene (DBU) / triethylamine / diisopropylamine (1 equiv.)	Dichloromethane (DCM), rt, 1 h	1.0	*0.0

* ***16*** *was unobserved due to its rapid fragmentation into the α-methylated-γ-diketone* ***25***

\# *The product ratios were determined by* ^1H *NMR analysis of the crude reaction mixture*

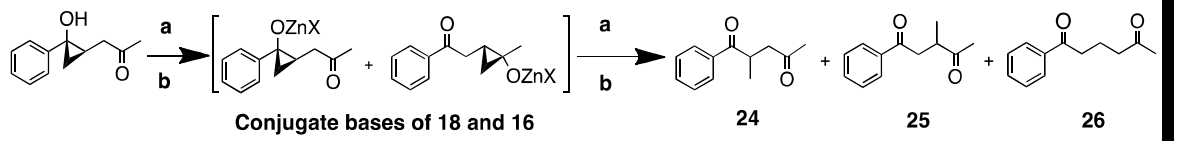
The results provided in **Table 3** indicate that rearrangement of the aryl cyclopropanol **18** using diethylzinc resulted in a mixture of 1 : 1 ratio of the regioisomeric cyclopropanols **18** and **16**. However using reaction conditions involving counterions other than zinc, the rearrangement

resulted in a 1 : 0.5 mixture of the regioisomeric cyclopropanols **18** and **16**. This unexpected product ratio may be obtained due to the fragmentation of **16** under the reaction conditions to yield alternate products like α-methylated-γ-diketone **25** and the chain extended δ-diketone **26**. A small amount of the β-methyl-γ-diketone **24** was also formed in the course of the reaction. This is proposed to occur from the ring cleavage of the aryl cyclopropanoxide (i.e. conjugate base of **18**).

Entry-6 of **Table 3** indicated that no rearrangement of the regioisomeric aryl cyclopropanol **18** occurred when using bases like DBU, triethylamine and diisopropylamine. Future studies would involve focussing the use of non-ionic super bases e.g. Verkade base and a Schwesinger phosphazene base to shift the equilibrium in the forward direction.[80,81]

The general nature of the *cyclopropanoxide rearrangements* was confirmed once again by subjecting the aryl cyclopropanol **18** to specified reaction conditions for extended time periods. The effect of the counterions on cyclopropanoxide rearrangements for time periods ≥3h are listed down in **Table 4**. It is worth noting in entries 1 and 2 of **Table 4** that rearrangement of the aryl cyclopropanol **18** using diethylzinc resulted in increased amounts of the regioisomeric methyl cyclopropanol **16** within the product mixture. Similar results were observed when diiodozinc (ZnI_2) was used in combination with diethylzinc to facilitate the rearrangement. However the product ratios obtained for the rearranged cyclopropanols **18** and **16** using reaction conditions involving counter ions other than zinc (entries 3 to 7) were consistently similar throughout the experiment. Entry 8 illustrated that attempts to facilitate cyclopropanoxide rearrangements using DBU and a catalytic amount of Lewis acid like diiodozinc (ZnI_2) did not provide access to the methyl cyclopropanol **16**, although evidence (vide-infra) was obtained that suggested the rearrangement was taking place.

Table 4: Cyclopropanoxide rearrangement and ring fragmentation of **18** and **16** under extended reaction times



Conjugate bases of 18 and 16 — **24** — **25** — **26**

Entry	**Reagents (a) / Reaction Conditions (b)**	**Ratio of** (18)	**Ratio of** (16)	**Ratio of** (24)	**Ratio of** (25)	**Ratio of** (26)
1.	Diethyl zinc (Et_2Zn) / Dichloromethane (DCM), rt, 12 h	0.5	1	0.1	0.2	0.4
2.	Diethyl zinc (Et_2Zn) and diiodo zinc (ZnI_2) / Dichloromethane (DCM), rt, 12 h	0.2	0.3	0.3	0.7	1
3	Methylmagnesium bromide (CH_3MgBr) / Tetrahydrofuran (THF), rt, 12 h	1	0.0	0.4	0.6	0.0
4.	Di-n-butyl magnesium [$(C_4H_9)_2Mg$] / Dichloromethane (DCM), rt, 3-4 h	1	0.3	0.5	0.0	0.5
5.	Sodium hydride (NaH) / Tetrahydrofuran (THF), rt, 12 h	1	0.4	0.0	0.2	0.6
6.	Potassium t-butoxide ($t\text{-}BuO^-K^+$) / Tetrahydrofuran (THF), rt, 2-5 h	0.7	0.2	0.3	1	1
7.	Lithium diisopropylamide (LDA) / Tetrahydrofuran (THF), rt, 12 h	1	0.5	0.0	0.5	0.5
8.	1,8-Diazabicyclo [5.4.0] undec-7-ene (DBU) + ZnI_2 (Cat.) / Dichloromethane (DCM), rt, 5 h	1	0.0	0.7	0.3	0.0

** The product ratios were determined by ^1H NMR analysis of the crude reaction mixture*

The formation of ring-fragmented derivatives **24**, **25** and **26** within the homologation-cyclopropanation reaction of β-diketones had not been reported during the initial cyclopropanol rearrangement studies conducted earlier within the Zercher group and as a result became the subject of investigation. The product mixture resulting from the cyclopropanoxide rearrangement of **18** was also studied.

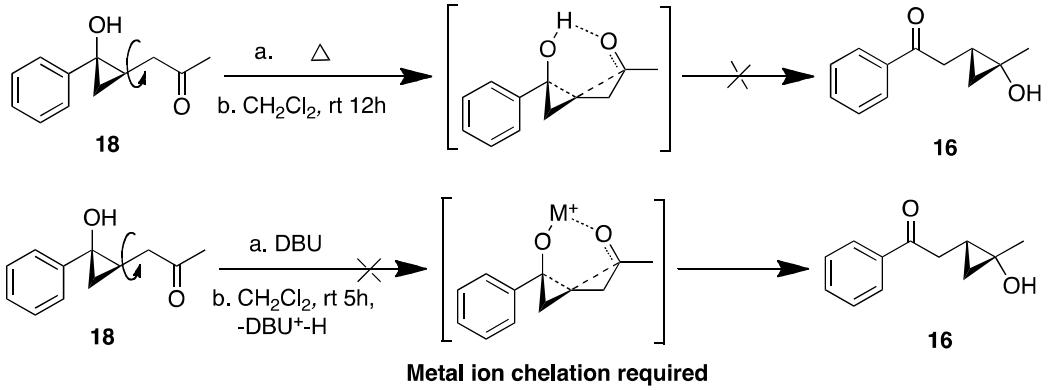
The results obtained from the cyclopropanoxide rearrangements observed under the reaction conditions specified in **Tables 3** and **4** also led to the conclusion that diethylzinc (i.e. influence of the zinc counter ion) facilitates a clean interconversionof the aryl cyclopropanol **18** to the methyl cyclopropanol **16** when short reaction times are used. Extended reaction times result in fragmentation of both regioisomeric cyclopropanoxides (i.e. *conjugate bases of* **18** and **16**) into the chain-extended δ-diketone **26** and a small amount of the β-methylated-γ-diketone **24**.

Incorporation of diiodozinc with long reaction times results in a 1 : 0.7 : 0.3 mixture of the chain-extended δ-diketone **26** along with α-and β-methylated-γ-diketones **24** and **25**. These results are consistent with the results reported for the ring fragmentation of 1, 2-diphenylcyclopropanol using lewis acids wherein 1,2-bond cleavage far exceeds 1,3-bond cleavage in both *cis* and *trans* isomers.[35,41,55]

It is also evident from **Tables 3** and **4** that counterions other than zinc (i.e. Na, K and Li) were able to facilitate interconversion of the regioisomeric cyclopropanoxides (i.e. conjugate base of **18** to **16**), However the cyclopropanoxide rearrangement that resulted in a 1 : 0.4 product mixture of the regioisomeric cyclopropanoxides (i.e. conjugate bases of **18** and **16)**, is competitive with ring fragmentation to yield the chain extended δ-diketone **26** as the major product along with a mixture of α- and β-alkylated-γ-diketones **24** and **25.**

On the contrary, cyclopropanoxide rearrangements using two different organomagnesium reagents (i.e. influence of magnesium counterion) surprisingly yielded different results. The use of di-n-butylmagnesium (1.0 M in heptane) resulted in the formation of a 0.5 : 0.5 mixture of extended δ-diketone **26** and β-alkylated γ-diketone **24**. Methyl Grignard (1.0 M in diethyl ether) on the other hand resulted in the formation of a 0.4 : 0.6 mixture of α- and β-methylated-γ-diketones. The results obtained in both cases were surprisingly different and hence require further investigation.

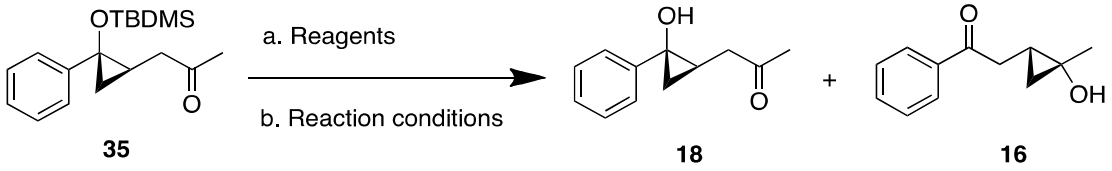
Thermal rearrangements of the aryl cyclopropanol **18** performed by refluxing **18** dissolved in dichloromethane (DCM) resulted in no cyclopropanoxide rearrangements. The absence of cyclopropanoxide rearrangements using non-nucleophilic bases (e.g. DBU, triethylamine, diisopropylamine and hunig's base) and under refluxing conditions led us to conclude that involvement of a metal counterion might be necessary to facilitate the rearrangement (**Scheme 3.32**).



Scheme 3.32: Proposed thermal and DBU-mediated rearrangement of the aryl cyclopropanol **18**

Deprotection of TBDMS ether **35** of the aryl cyclopropanol **18** using Lewis acids like zinc triflate [$Zn(OTf)_2$] supported the involvement of metal ion chelation during cyclopropanoxide rearrangements (**Table 5**).

Table 5: Zinc triflate mediated deprotection of silyl ether **35** followed by cyclopropanoxide rearrangement



Entry	Reagents / Equivalents	Reaction Conditions	Ratio of (18)	Ratio of (16)	Ratio of (35)
1.	Zinc triflate [$Zn(OTf)_2$] / (0.5 equiv.)	Dichloromethane (DCM), rt, 40 min	1	0.5	0.5
2.	Zinc triflate [$Zn(OTf)_2$] / (1.1 equiv.)	Dichloromethane (DCM), rt, 35 min	1	1	-

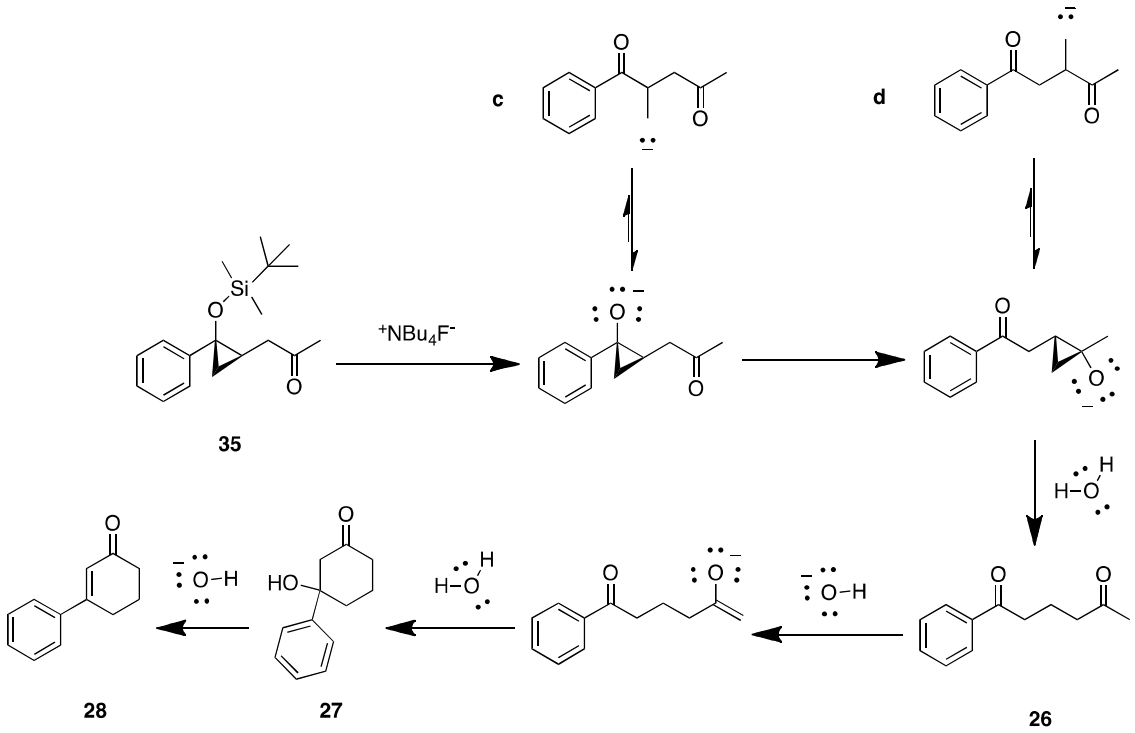
** The product ratios were determined by ^1H NMR analysis of the crude reaction mixture*

The use of 0.5 equivalents (i.e. 5 mole percent) of zinc triflate resulted in partial deprotection of **35** followed by cyclopropanoxide rearrangement. However use of 1.1 equivalent (i.e. 10 mole percent) of zinc triflate resulted in complete deprotection of the TBDMS ether **35** yeilding a 1 : 1 mixture of the regioisomeric cyclopropanols (**18** and **16**), thereby suggesting that deprotection of the TBDMS ether **35** was limited to the molar equivalents of zinc triflate employed during the reaction.

A similar deprotection strategy of **35** using TBAF (1M in THF) for 12 h resulted in the formation of a 1 : 0.7 : 0.5 mixture of the β-methylated-γ-diketone **24**, the methyl cyclopropanol **16** and the chain extended δ-diketone **26**. The initial results obtained indicated that equilibration of cyclopropanoxides could also be facilitated without the involvement of metal ion chelation. Increased formation of **24** was suggestive of the γ-keto aryl cyclopropanoxide (i.e. *conjugate base of* **18**) in equilibrium with its homoenolate **c**. Formation of methyl cyclopropanoxide (i.e.

conjugate base of **16**) was believed to result from cyclopropanoxide rearrangement. Formation of **26** was believed to result from the ring fragmentation of methyl cyclopropanoxide followed by proton abstraction from trace amounts of moisture.

Deprotection of **35** using TBAF (1M in THF) for 16 h resulted in the formation of a 1 : 1 : 1 mixture of the δ-diketone **26**, the *ketol* **27** and the *enone* **28**. Formation of the *ketol* **27** and the *enone* **28** within the 16 h crude reaction mixture was believed to result from an intramolecular aldol reaction of the chain extended δ-di ketone **26** (**Scheme 3.33**).

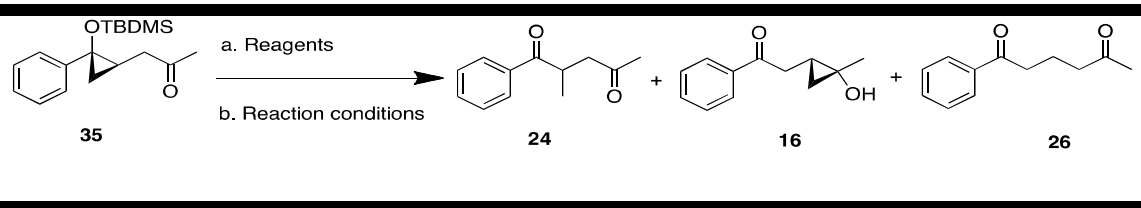


Scheme 3.33: Proposed mechanism for TBAF-mediated deprotection and rearrangement of silyl ether **35**

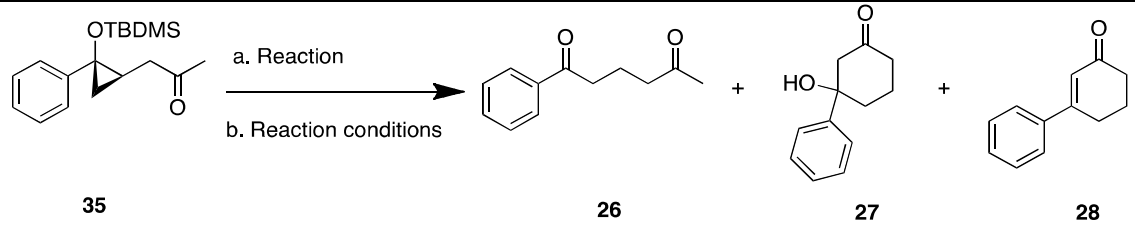
It is worth noting that although homoenolate **d** likely exists in equilibrium with the methyl cyclopropanoxide, fragmentation of the cyclopropanoxide to **26** was necessary for product formation. The reason for this selective fragmentation would require more investigation. The

results obtained for TBAF-mediated deprotection of the silyl ether 35 are illustrated in **Table 6**. The mechanisitic pathway for the above reaction appears to be similar in nature to the potassium *tert*-butoxide (t-BuO$^-$K$^+$) mediated cyclopropanoxide rearrangement (*observed earlier in* **Scheme 3.10)**.

Table 6: Tetra-n-butylammonium fluoride (TBAF) mediated deprotection of silyl ether **35** followed by cyclopropanoxide rearrangement



Entry	Reagents / Equivalents	Reaction Conditions	Ratio of (16)	Ratio of (24)	Ratio of (26)
1.	Tetra-n-butylammonium fluoride (1M in THF) / (1 equiv.)	Tetrahydrofuran (THF), rt, 12 h	0.7	1	0.5



Entry	Reagents / Equivalents	Reaction Conditions	Ratio of (16)	Ratio of (24)	Ratio of (26)
2.	Tetra-n-butylammonium fluoride (1M in THF) / (1 equiv.)	Tetrahydrofuran (THF), rt, 16 h	1	1	1

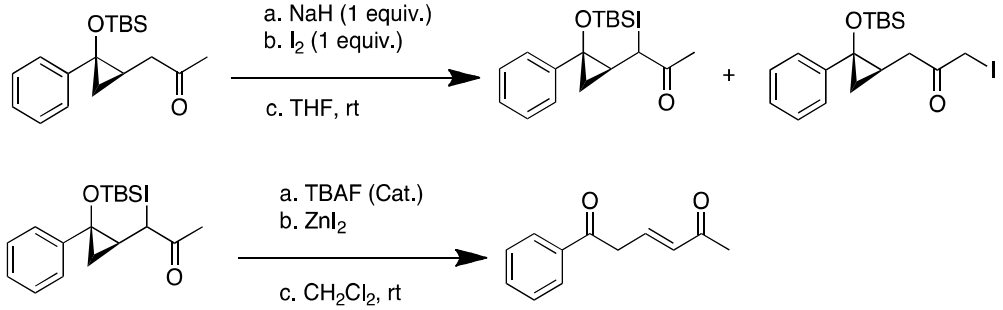
** The product ratios were determined by ^{1}H NMR analysis of the crude reaction mixture obtained after column chromatography*

The only difference between the two pathways is that the latter is proposed to proceed through a seven-membered metal-ion (i.e. K^+ counter-ion) chelated transition state. Since no metal-ion

chelation exists within TBAF-mediated cyclopropanoxide rearrangements, a direct comparison with the reaction kinetics of the zinc carbenoid-mediated HCRF reaction would likely require extensive computational studies.

4.0 Future work towards zinc carbenoid-mediated homologation and cyclopropanoxide rearrangements:

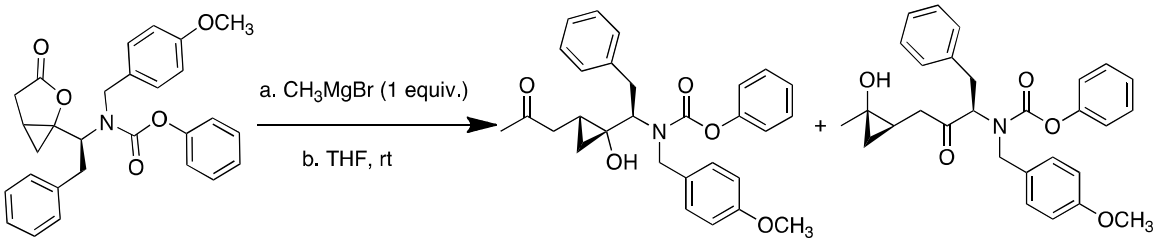
In the long run a better understanding of the cyclopropanoxide rearrangements is important. As more complex cyclopropanols are formed and exposed to rearrangement conditions, the stereochemical course of the reaction may depend upon the reaction conditions. Latent enolates generated from the chain extension of β-keto esters and imides have been used to trap molecular halogens, like iodine, for the preparation of α, β-unsaturated-γ-keto esters and amides.[11,12,26] The regioselective preparation of α, β-unsaturated-γ-diketones using α-halogenated regioisomeric cyclopropanoxides constitutes a direction of future study (**Scheme 3.34**).



Scheme 3.34: Proposed pathways for the preparation of α, β-unstaturated-γ-diketones using TBDMS ether **35**

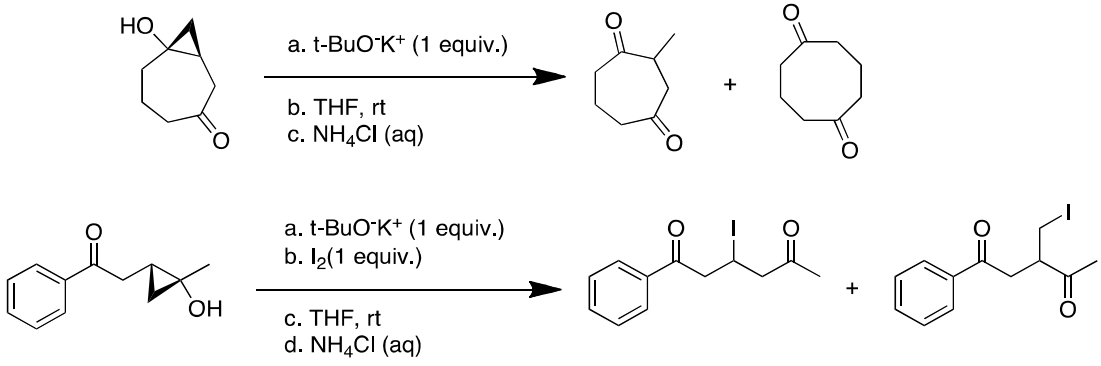
Future prospects in this area could also be directed towards designing novel amino acid derived cyclopropanol peptide isosteres. The synthesis of phenylalanine-derived cyclopropanols is currently under investigation.[33] Chiral cyclopropanols will provide the opportunity to study the

diastereoselectivity of the cyclopropanol rearrangements reported herein (**Scheme 3.35**). A better understanding of the rearrangement would enhance the opportunities to prepare cyclopropanol containing peptide isosteres (e.g. α,β-unstaturated-γ-diketone) for competitive inhibition of targeted enzymes.



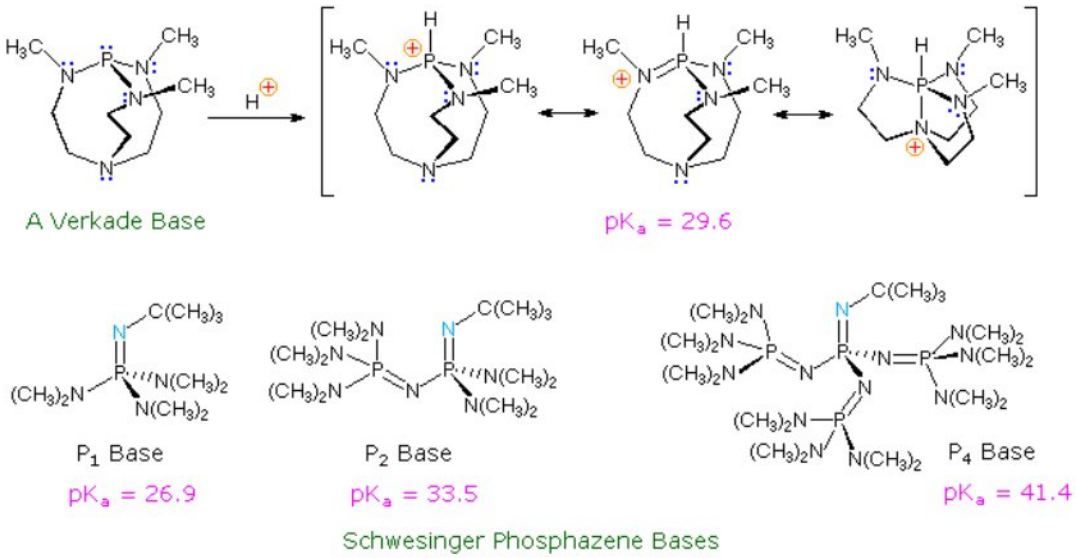
Scheme 3.35: Proposed pathway for cyclopropanoxide rearrangement using phenylalanine derived cyclopropanoxide

The results obtained in the studies of homologation-cyclopropanation ring fragmentation chemistry (HCRF) of acyclic diketones could also be used to develop conditions by which electrophiles could be trapped or by which ring expansion protocol could be developed (**Scheme 3.36**).



Scheme 3.36: Proposed pathway for ring expansion and electrophile capture

As discussed earlier in **Section 3.4**, rearrangement of aryl cyclopropanol **18** to the methyl cyclopropanol **16** using non-nucleophilic and sterically encumbered bases e.g. DBU, diisopropylamine, Hunig's base etc have not been quite successful. However use of non-ionic *superbases* e.g. Verkade[80] base and Schwesinger[81] phosphazene base to facilitate such a cyclopropanoxide rearrangement could be investigated.



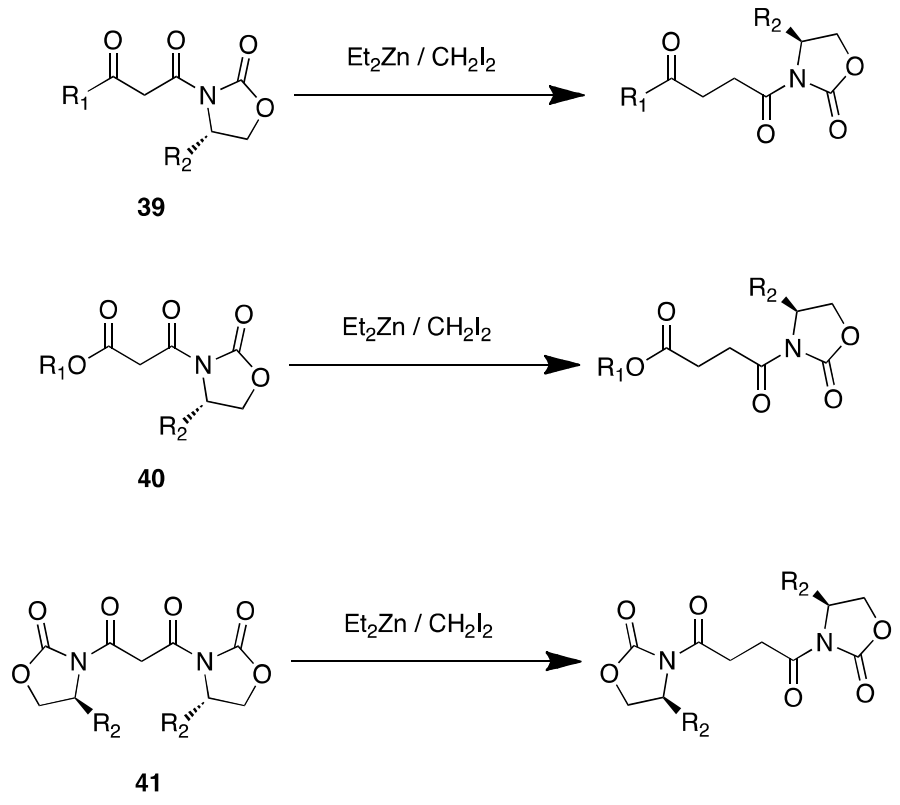
* *pKa's were measured in acetonitrile*

Figure 11: Proposed use of non-ionic superbases for facilitating cyclopropanoxide rearrangement.

Chapter 4

Tandem chain extension-aldol reaction and lactonization of α-carboxyester imides

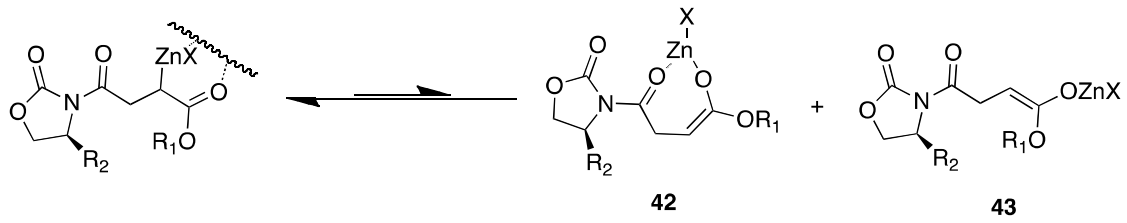
Zinc-carbenoid mediated chain extension of β-keto imides (**39**)[10,59,60], α-carboxyester imides (**40**)[14,15,60] and α-carboxydiimides (**41**)[16] have been investigated and, shown to undergo zinc-carbenoid mediated homologation thus widening the scope of the reaction (**Scheme 4.0**).



Scheme 4.0: Zinc-carbenoid mediated homologation of variety of β-dicarbonyl substrates

Tandem chain extension aldol reactions have been investigated extensively within the Zercher group. As described earlier in chapter I the Reformatsky-like zinc organometallic intermediate formed during the chain extension of β-keto esters and amides are used to effectively trap a variety of aldehydes, resulting in the preferential formation of the *syn*-aldol.[9] The reactivity of these chain extended intermediates with aldehydes likely requires isomerization to the more reactive oxygen-bonded zinc enolate.[61,62,63]

Lai[9] reported that the O-bound ester enolate generated from the β-keto imide **39** participates in aldol reactions most likely through the Z-enolate as described in chapter I (**Scheme 1.29**). Based on Lai's initial results on tandem chain-extension aldol reaction of β-keto imides, Lin[60] proposed that tandem chain extension aldol reactions could also be investigated using α-carboxyester imides **40** wherein the Z-isomer will favor the formation of the *syn*–aldol via a closed (Zimmerman-Traxler) transition state (**Scheme 4.1**).

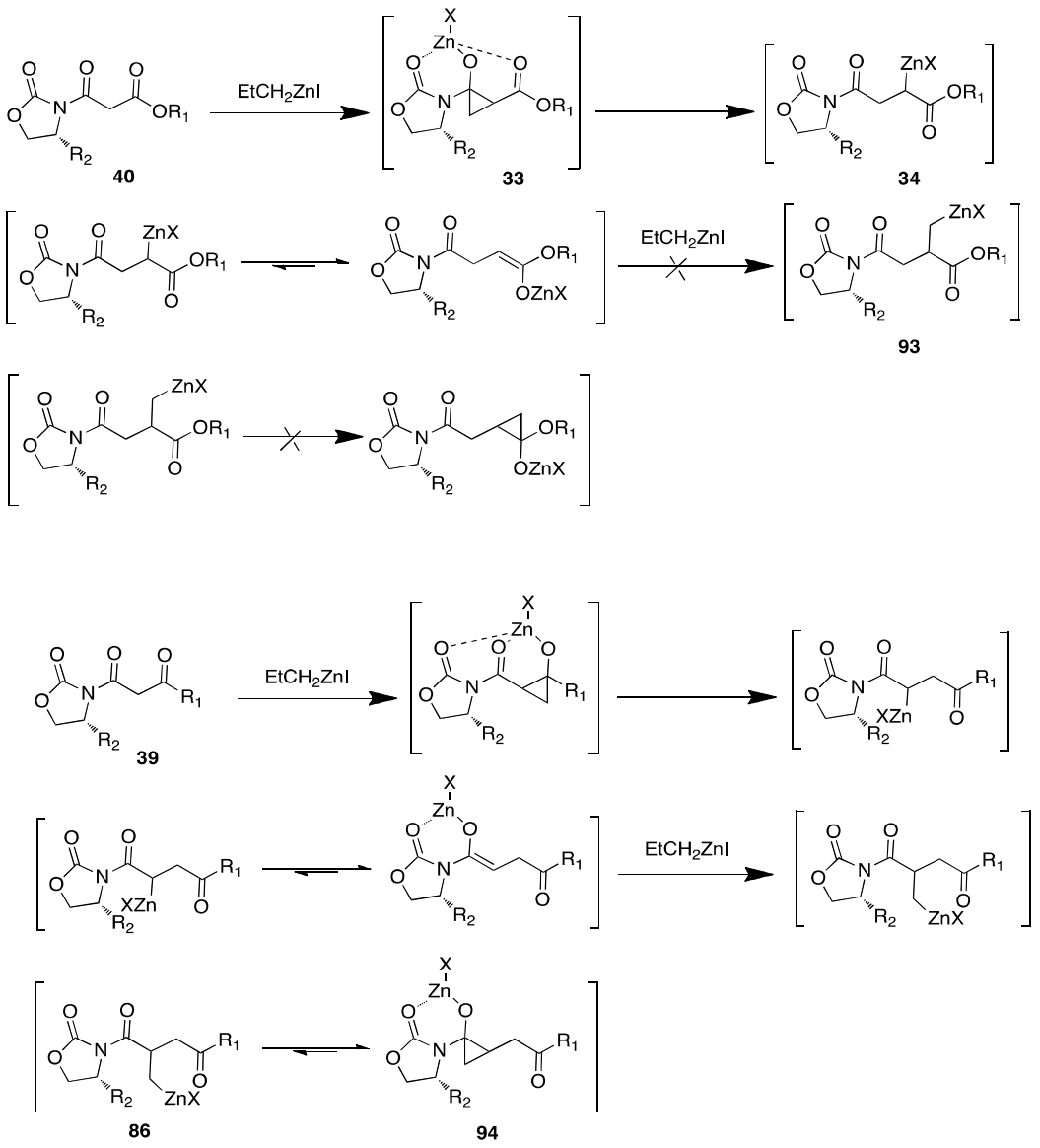


Scheme 4.1: Dissociation of the C-bound zinc enolate to the O-bound zinc enolates **42** and **43**

4.1 Tandem chain-extension-aldol reactions and lactonization:

Chain homologation of α-carboxyester imides **40** was investigated within the Zercher group using the Furukawa's carbenoid ($EtCH_2ZnI$). The reaction, however, didn't result in the formation of the chain extended cyclopropanoxide involving the imide functionality of the chiral auxillary, which was previously observed for β-keto imides by Lin.[46,60] The difference in

reactivity is explained based on the cyclization of the initially formed homoenolate into the most electrophilic carbonyl functionality of the β-dicarbonyl substrate in either case (**Scheme 4.2**).

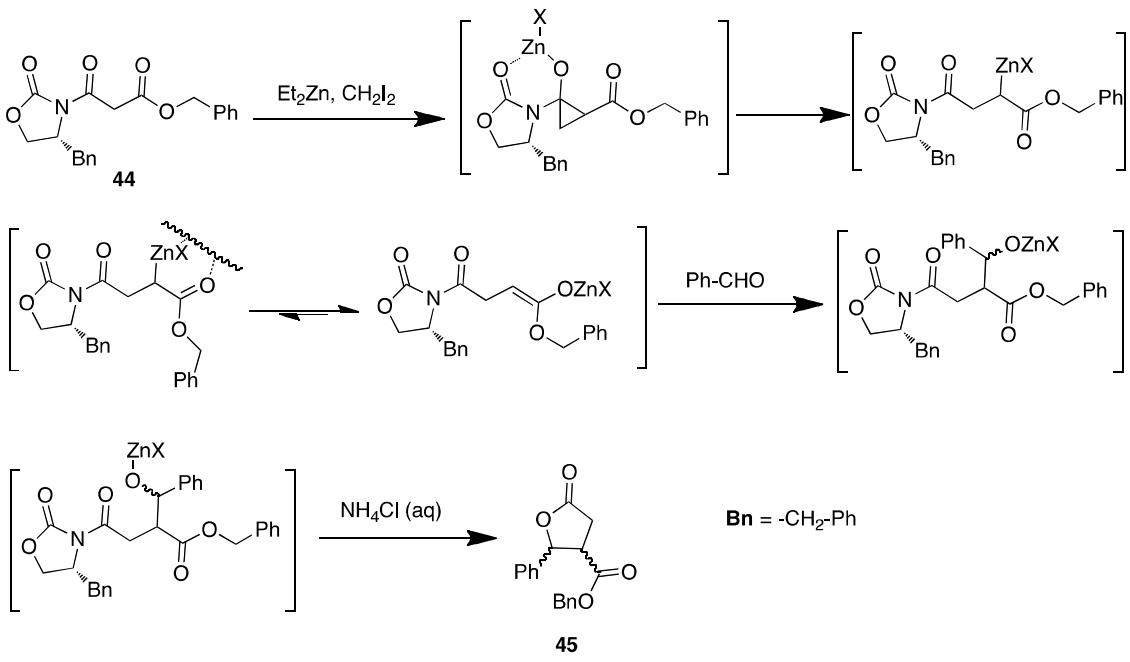


Scheme 4.2: Regioselective cyclopropanation in β-keto imides **39** versus α-carboxyester imides **40**

The donor acceptor cyclopropane **33** resulting from **40** fragments to yield the chain-extended zinc enolate **34**, which upon protonation completes the chain-extension reaction with excess

Furukuwa's carbenoid would lead to the formation of the carbon-bound zinc homoenolate **93**. The homoenolate is unlikely to cyclize into the carbonyl carbon of the ester functionality. In the study of **39**, Lin[60] proposed that the formation of the cyclopropane intermediate **94** results from cyclization of **86** into the electrophilic imide carbonyl. The stability of **94** involving the imide functionality was attributed to the complexation zinc cyclopropanoxide, with the (a)chiral auxiliary (i.e. oxazolidinone).

Lin[60] extended his work on α-carboxyester imides by subjecting **44** to tandem chain homologation-aldol reaction conditions. A single unidentified diastereomeric lactone **45** was obtained when the chain extended ester enolate of **44** was trapped with benzaldehyde to obtain the aldol (**Scheme 4.3**).



44 **45**

Scheme 4.3: Tandem chain extension-aldol reaction of α-carboxyester imide **44**

4.2 Application of Zimmerman-Traxler model towards lactone formation:

Following the preliminary work of Lai[9] and Lin,[14] Sadlowski[15] reported the formation of a mixture of diastereomeric lactones using a series of aliphatic and aromatic aldehydes. The diastereocontrol within the tandem chain-homologation aldol reactions using α-carboxyester imides was explored. Sadlowski indicated that *syn*-aldols would be necessary for the formation of a *trans* lactone **51**, whereas the *anti*-aldols would yield a *cis* lactone **53**. Sadlowski reported the *trans* lactone would be the major isomer to form from the Z-enolate **42** (*as described earlier in* **Scheme 4.1**) that reacts through a kinetically–controlled *syn*-aldol reaction. Studies by Aiken[21] revealed that the *syn*-selectivity is contingent on the presence of the γ-ketone, presumably resulting in a biasing towards formation of an intermediate Z-enolate. With such enolate selectivity, the diastereocontrol within the lactone would be determined by the facial selectivity of the aldehyde in the aldol reaction (**Figure 12**).

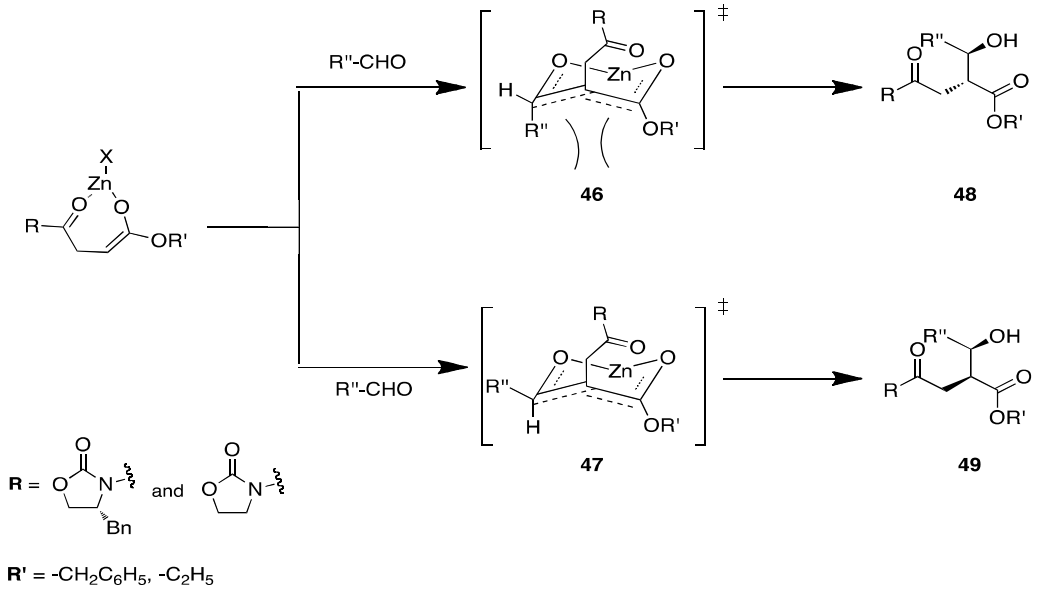


Figure 12: Zimmerman-Traxler closed transition state model for Z-enolate of tandem chain extension aldol reaction

The approach of the aldehydic substituent (R'') to the Z-enolate in a pseudo-equatorial position, as illustrated in **47**, favors the formation of the *syn*-aldol **49**. Approach of (R'') in a pseudo-axial position, as illustrated in **46,** would result in the formation of the *anti*-aldol **48**. It is rationalized that undesirable 1,3-diaxial interactions within the transition state renders the *anti*-aldol less favorable.[75] Bond rotation and intramolecular acylation converts the *syn* and *anti*-aldol products to the *trans* and *cis*-lactones, respectively (**Figure 13**).

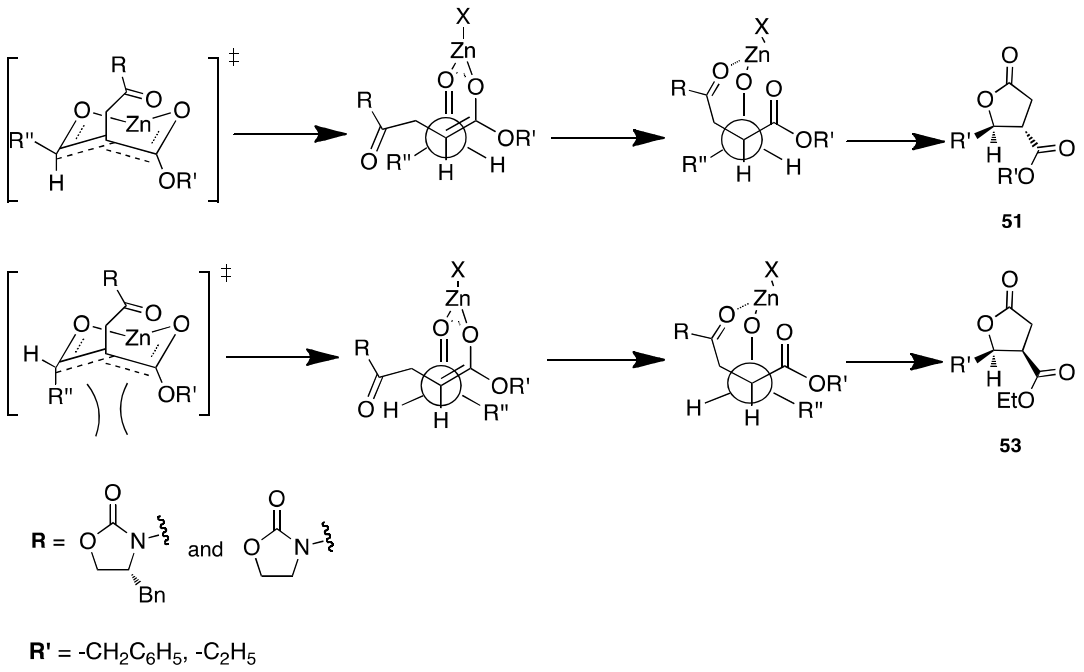
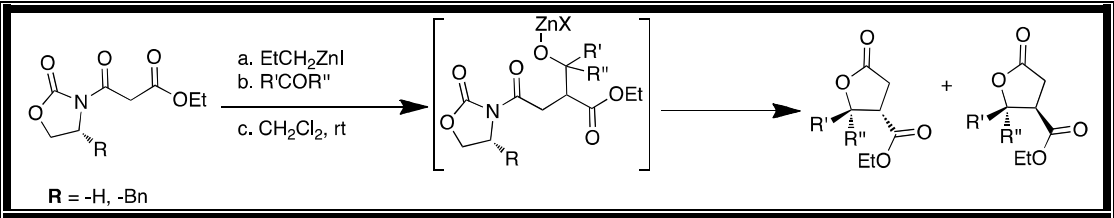


Figure 13: Conversion of aldol products to lactones

4.3 Initial efforts and research objective:

Sadlowski[15] reported excellent diastereoselective lactone formation when using aromatic aldehydes, which provided a greater *trans* : *cis* ratio compared to the aliphatic aldehydes (**Table 7**). However, the distribution of product ratios in the crude reaction mixture was not determined using NMR analysis. Sadlowski's analysis on diastereocontrol was based on ratios of purified products only.

Table 7: Ratios of *cis* and *trans* lactones obtained from homologation-cyclopropanation of α-carboxyester imides[15]



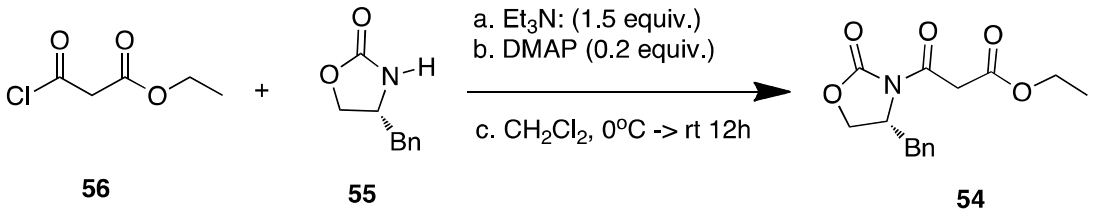
Entry	R	R'	R''	Trans isomer	Cis isomer	Yield %
1.	-H	$-C_6H_5$	-H	3	1	67
2.	-H	$-C_6H_5$-*p*-OCH_3	-H	3	1	50
3.	-H	$-C(CH_3)_3$	-H	7	1	90
4.	-H	2-Furyl	-H	12	1	58
5.	-H	$-(CH_2)_4CH_3$	-H	2	1	80
6	-H	$-(CH_2)_3CH_3$	-H	1	1	41

* *cis-isomers were never isolated from the crude reaction mixture.*

The diastereomeric lactones listed in **Table 7** may be interest as derivatives of paraconic acids.[65-68] Synthetic procedures are reported in the literature for the formation of these diastereomeric γ-butyrolactones, although formation of the *cis*-lactone isomer is usually preferred over their *trans* counterparts.[65-67] However initial results reported for tandem chain extension-aldol reaction and lactonization of α-carboxyester imides[60] suggests that the *syn*-aldol preference would favor the preferential formation of the *trans* lactones over their *cis*

counterparts. This difference in diasteroselective product formation was the major focus of our study. Stereochemical assignments of product lactones within our studies were based on comparison to literature reports, when available. For compounds not reported in the literature, assignments are based on the most relevant analogous compounds.[65-66]

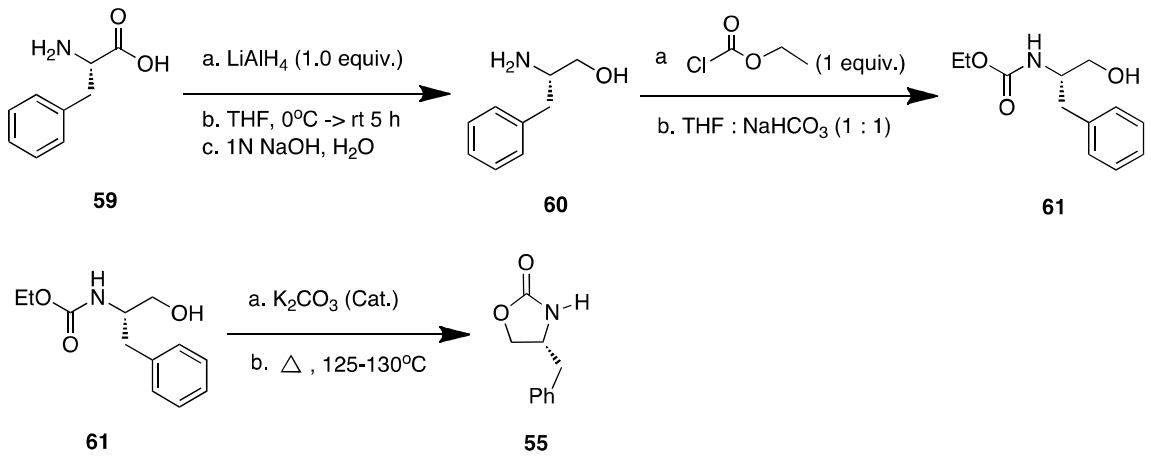
The formation of diastereomeric lactones and their distribution within the crude reaction mixture was investigated by subjecting the α-carboxyester imide **54** to tandem chain-extension aldol (TCEA) and lactonization reactions using different aliphatic and aromatic aldehydes and ketones. The α-carboxyester imide **54** was prepared by subjecting the chiral oxazolidinone **55** to react with ethyl malonyl chloride **56**. Catalytic amount of 4,4'-dimethylaminopyridine (DMAP) was used to form the intermediate acyl pyridinium salt. Triethylamine was employed to couple the chiral oxazolidinone **55** with the acyl pyridinium intermediate of **56** through formation of an intermediate *ketene*. Triethylamine was used to scavenge the hydrochloric acid (HCl) byproduct formed during the reaction (**Scheme 4.4**).[64,76]



56 **55** **54**

Scheme 4.4: Preparation of α-carboxyester imide **54** using the chiral oxazolidinone **55**

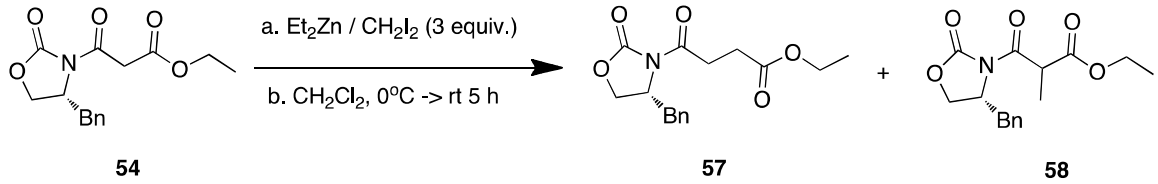
The chiral oxazolidinone **55** was prepared by a three-step process (**Scheme 4.5**) The first step involved the reduction of the L-phenylalanine **59** to the (*S*)-amino alcohol **60**.[77] The second step involved subjecting the (*S*)-amino alcohol **60** to react with ethylchloroformate resulting in the formation of the substituted carbamate **61**.[78] The third step involved an intramolecular cyclization of **61** using potassium carbonate to yield **55**.[79]



59 60 61 61 55

Scheme 4.5: Three-step synthetic route for the preparation of the chiral oxazolidinone **55**

The α-carboxyester imide **54** was then subjected to chain homologation reaction conditions using the Furukawa's carbenoid ($EtZnCH_2I$) for a period of 5 h. The crude reaction mixture on NMR analysis indicated the presence of the chain extended product **57** along with minor amounts of the α-methylated material **58** (**Scheme 4.6**). The formation of the homoenolate **58** was consistent with the involvement of a homoenolate within the traditional chain-homologation reaction mechanism, as proposed initially by Eger and Zercher.[30]

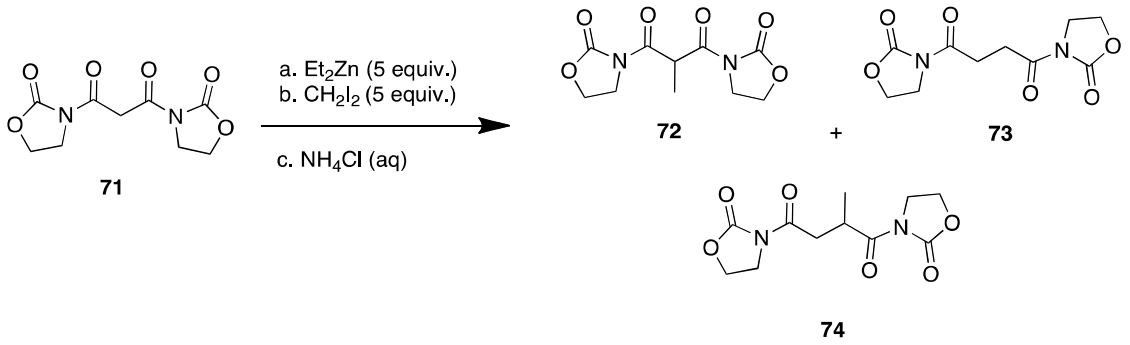


54 57 58

Scheme 4.6: Chain-homologation of α-carboxyester imide **54** yielding the chain extended product **57** and the α-methylated product **58**

The formation of **58** was believed to result from the zinc-bound homoenolate abstracting one of the methylene protons from the starting material **54** or getting quenched owing to trace amounts of moisture in the solvent.

Henderson[16] reported similar observations in studies of malonyl bisimide **71**. Subjecting **71** to five equivalents of Furukawa's carbenoid yielded the α-methylated bisimide **72**, the chain extended bisimide **73** and the α-methylated chain extended bisimide **74**. In Henderson's studies, no ideal time was identified for the addition of an aldehyde, since formation of **74** was resulting prior to the complete consumption of the starting material (**Scheme 4.7**).



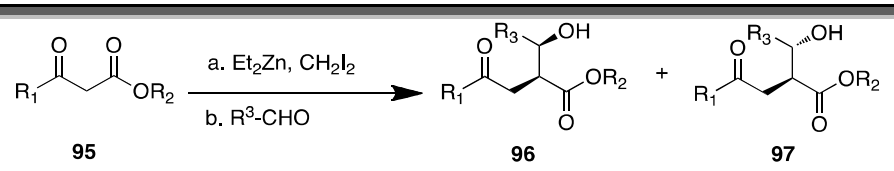
Scheme 4.7: Zinc-carbenoid mediated chain-homologation of the malonyl bisimide **71**

As a continuation of studies of Lin[60] and Sadlowski[15], the α-carboxyester imide **54** was subjected to homologation-cyclopropanation reaction conditions a second time. However this time the goal was to trap the chain extended ester enolate of **57** with different aldehydes and ketones to obtain a mixture of diastereomeric lactones and characterize their presence within the crude reaction mixture by NMR.

4.4 Results and Discussion:

Diastereomeric lactones derived from γ-phenyl paraconic acids have found widespread applications especially in the field of medicinal chemistry, as well as in the cosmetic and chemical industry.[70] Diastereoselective tandem chain extension-aldol reactions using β-keto esters and imides were investigated in the Zercher group (**Table 8**).

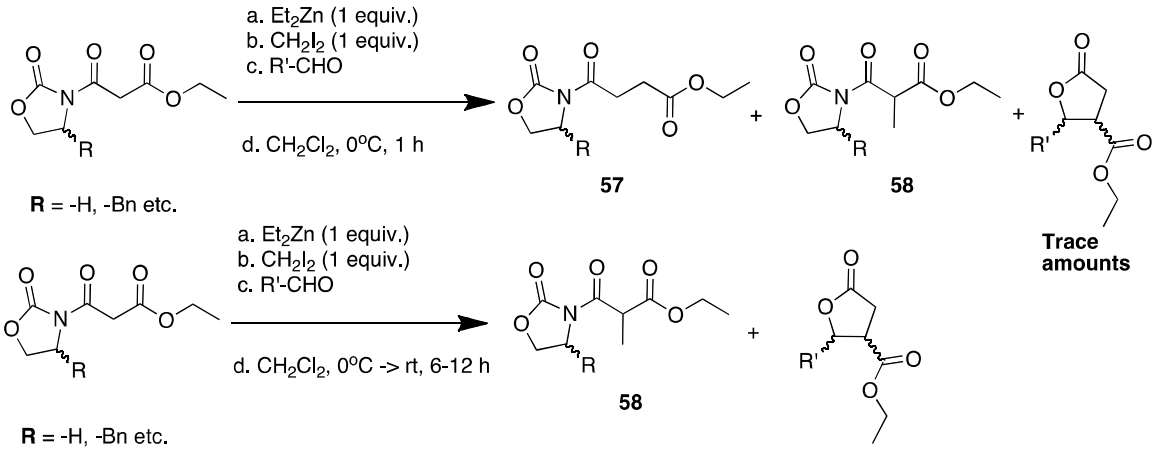
Table 8: Tandem chain extension-aldol reaction of β-keto esters and amides



Entry	R^1	R^2	R^3	Yield %	*syn* : *anti*
1.	-t-Bu	-OMe	-Ph	97	12 : 1
2.	-t-Bu	-OMe	-Ar	61	9 : 1
3.	-Ar	-OEt	-Ar	57	7 : 1
4.	-Me	-OMe	-t-Bu	85	>20 : 1
5.	-Me	-OMe	-Ph	61	15 : 1
6.	-Me	-NPhMe	-Me	46	3 : 1

Diastereocontrol on the order of 10 : 1 was reported with predominant formation of the *syn* aldol isomer when using β-keto ester as the starting material.[9,21]

Performing the tandem chain extension-aldol protocol on α-carboxyester imides as the starting material resulted in the formation of lactones via intramolecular acylation. Extended reaction times were required for efficient formation of the diastereomeric mixture of lactones (**Scheme 4.8**). The tandem chain extension-aldol reaction followed by lactonization should result in product stereocontrol that mimics the diasterecontrol in the aldol reaction (*described earlier in* **Table 8**); however, the diastereoselectivity observed in previous studies[15] was lower than the diastereocontrol of the TCEA reactions illustrated in **Table 8**.



Scheme 4.8: Time-dependent tandem chain extension-aldol reaction and lactonization of α-carboxyester imide **40**

The formation of the α-methylated product **58** (i.e. **R** = -H) within the crude reaction mixture was attributed to insufficient electrophilicity of the imide carbonyl. The electrophilicity of the imide carbonyl was decreased by n-π conjugation of the non-bonding electron pair on the amide nitrogen with the π-system of the carbonyl group. The existence of partial double-bond character around the imide carbonyl was believed to impede the formation of the initial donor-acceptor cyclopropane intermediate, which is a requisite precursor for the formation of **57** (i.e. **R** = -H). Replacement of the achiral oxazolidinone (i.e. **R** = -H) with a chiral oxazolidinone (i.e. **R** = -Bn) resulted in decreased formation of the α-methylated product **58**. A possible explanation for the reduced formation of **58** (i.e. **R** = -Bn) was the relief of increased $A^{1,3}$-strain through bond rotation, which led to enhanced electrophilicity of the imide carbonyl (**Figure 14**).

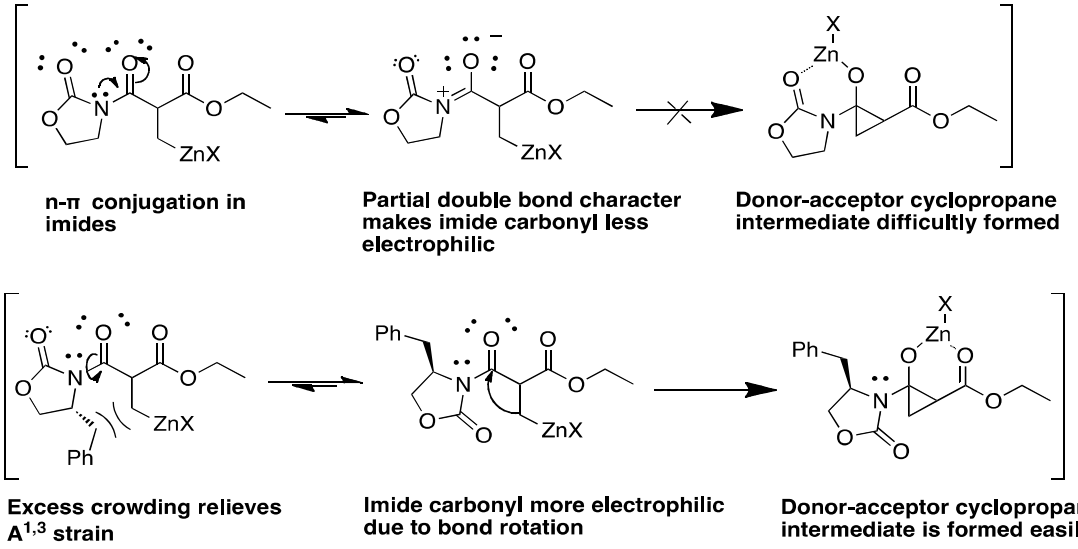
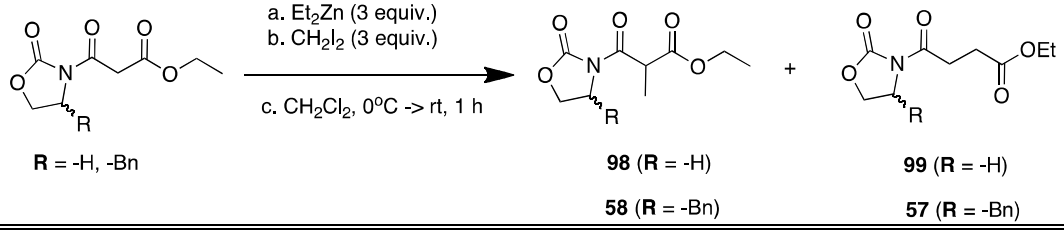


Figure 14: Relief of $A^{1,3}$-strain by using α-carboxyester imides employing a chiral auxiliary

The above explanation was supported by subjecting tha α-carboxyester imide **40** employing both achiral (i.e. R = -H) as well as chiral oxazolidinones (i.e. R = -Bn) to zinc-mediated chain extension for 1 h. Results obtained for the 1 h zinc-mediated chain extension reaction are illustrated in **Table 9**

Table 9: Furukawa carbenoid-mediated chain extension of the α-carboxyester imide

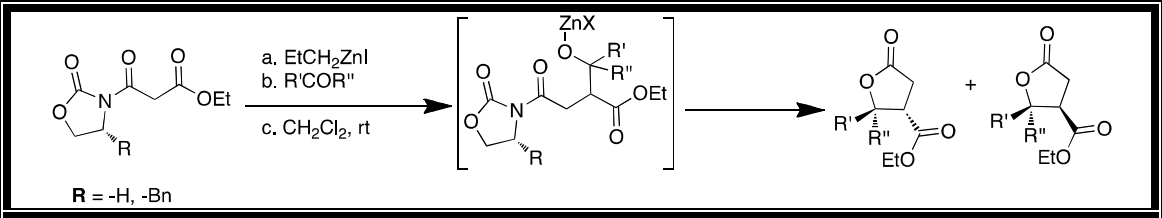


Entry	-R	Ratio of **98**	Ratio of **99**	% Composition	
				98 (R = -H)	**99 (R = -H)**
1.	-H	3	1	25	75
2.	-Bn	Ratio of **58**	Ratio of **57**	% Composition	
		1	3	**58 (R = -Bn)**	**57 (R = -Bn)**
				75	25

** The product ratios were determined using NMR studies*

Subjecting the α-carboxyester imide **(**R = -Bn**)** to tandem chain extension-aldol reaction conditions over a period of 12 h resulted in the formation of diastereomeric mixture of lactones (**Table 10**).

Table 10: Ratios and percent conversions of diastereomeric γ-substituted lactones prepared from tandem chain extension-aldol reaction of α-carboxyester imides



Entry	R	R'	R''	Diastereomeric ratios		% Yields	
				***Trans* isomer**	***Cis* isomer**	***Trans***	***Cis***
1.	-Bn	$-C_6H_5$	-H	3	1	33	17
2.	-Bn	$-C_6H_5$-*p*-OCH_3	-H	3	1	45	19
3.	-Bn	$-C(CH_3)_3$	-H	9	1	39	18
4.	-Bn	$-(CH_2)_2$-Ph	-H	*	5	*	37
5	-Bn	$-CH_3$	$-CH_3$	-	-	#	#
6	-Bn	$-C_6H_5$-*p*-Cl	$-CH_3$	8.5	1.5	46	21
7	-H	$-C_6H_5$-*p*-CH_3	-H	8	1	41	15
8	-H	2-Furyl	-H	12	1	45	*

** Product was never isolated*

 # Only one product formed with a yield of 74%

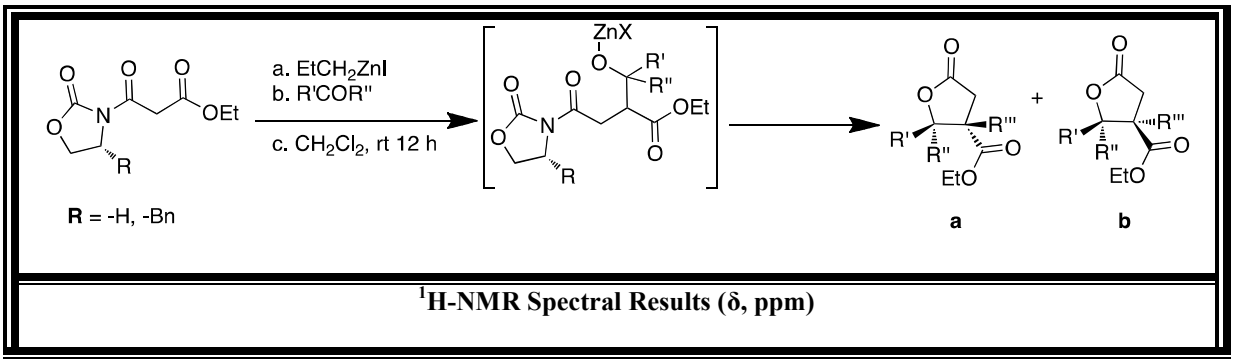
a). *Diastereomeric ratio determined by ^{1}H NMR of the crude reaction mixture*

The ratios of the diastereomeric lactones were determined from NMR of the crude reaction mixture. Results provided in entries **1** and **2** illustrated that the ratios of diastereomeric lactones obtained for the 12 h crude reaction mixture were consistent with results reported initially by Sadlowski[15].

Entries **3** till **8** indicated that the *trans* lactone was obtained in major amounts as opposed to the *cis* lactone, which was consistent with the diastereocontrol in tandem chain extension-aldol reaction of β-keto esters and imides. Entry **4** revealed that tandem chain extension-aldol reaction and lactonization resulted in the formation of both *cis* and *trans* lactones. However, the *cis* lactone was the only product obtained in 50% yield. The trans lactone was never isolated from the crude mixture. Results tabulated within entry 5 revealed the formation of only one product lactone in 74% yield.

NMR analysis of the crude reaction mixture resulting from tandem chain extension-aldol reaction and lactonization also revealed the formation of the chiral oxazolidinone **55** as one of the byproducts which was in accordance with the reaction mechanism and formation of product lactones. Evidence for the configurational assignment of the product lactones was obtained by the comparison of their NMR results against the literature reported results (**Table 11**).[65-67]

Table 11: ^{1}H-NMR chemical shift results for the diastereomeric lactones **a** and **b** prepared from tandem chain extension-aldol reaction of α-carboxyester imides



^{1}H-NMR Spectral Results (δ, ppm)

Entry	R'	(δ, ppm)	R''	(δ, ppm)	R'''	(δ, ppm)	α-CH_2 (δ, ppm)	–OEt (δ, ppm)
1a[65-66]	-C_6H_5	7.54–7.28 (m)	-H	5.66 (d)	-H	3.38-3.26 (m)	3.01 (dd) and 2.91(dd)	4.24 (m) and 1.29 (t)
1b[65-66]	-C_6H_5	7.46–7.22 (m)	-H	5.76 (d)	-H	3.87-3.59 (m)	3.10 (dd) and 2.81(dd)	3.87-3.59 (m) and 0.87 (t)
2a[67]	-C_6H_5-*p*-OMe	7.37-6.83 (m) and 3.82 (s)	-H	5.58 (d)	-H	3.31(m)	3.00 (dd) and 2.91 (dd)	4.21 (tq) and 1.26 (t)
2b[67]	-C_6H_5-*p*-OMe	7.23-6.83 (m) and 3.80 (s)	-H	5.72 (d)	-H	3.94-3.58 (m)	3.10 (dd) and 2.78 (dd)	3.94-3.58 (m) and 0.92 (t)
3a[65]	-$C(CH_3)_3$	0.97 (s)	-H	4.42 (d)	-H	3.13 (ddd)	2.89 (dd) and 2.78 (dd)	4.29-4.12 (m) and 1.29 (t)
3b[65]	-$C(CH_3)_3$	1.03 (s)	-H	4.23 (d)	-H	3.31 (ddd)	2.80 (dd) and 2.66 (dd)	4.22-4.08 (m) and 1.28 (t)
4a*[67]	-$(CH_2)_2$-Ph	7.15-7.32 (m), 2.67-2.98 (m) and 1.95-2.19 (m)	-H	4.51-4.58 (m)	-H	3.35-3.52 (m)	3.00-3.10 (m) and 2.67-2.98 (m)	4.18 (q) and 1.25 (t)
4b[67]	-$(CH_2)_2$-Ph	7.41-7.13 (m), 2.80-2.61 (m) and 2.00-1.80 (m)	-H	4.60 (ddd)	-H	3.46-3.34 (m)	2.98-2.83 (m) and 2.80-2.61 (m)	4.21 (q) and 1.27 (t)
5[82-83]	-CH_3	1.61 (s)	-CH_3	1.36 (s)	-H	3.23-3.14 (dd)	3.09 (dd) and 2.70 (dd)	4.31-4.14 (m) and 1.27 (t)
6a	-C_6H_5-*p*-Cl	7.47–7.32 (m)	-CH_3	1.66 (s)	-H	3.46 (dd)	3.03 (dd) and 2.65 (dd)	4.37 – 4.20 (m) and 1.34 (t)
6b	-C_6H_5-*p*-Cl	7.38–7.22 (m)	-CH_3	1.89 (s)	-H	3.43 (dd)	2.99 (dd) and 2.85 (dd)	3.91-3.69 (m) and 0.99 (t)
7a	-C_6H_5-*p*-CH_3	7.26–7.19 (m) and 2.37 (s)	-H	5.62 (d)	-H	3.39-3.23 (m)	3.09 (dd) and 2.83 (dd)	4.22 (tdd) and 1.27 (t)
7b	-C_6H_5-*p*-CH_3	7.24–7.08 (m) and 2.34 (s)	-H	5.73 (d)	-H	3.91-3.61 (m)	3.10 (dd) and 2.78 (dd)	3.91-3.61 (m) and 0.91 (t)
8a#	2-Furyl	7.51-7.41 (m), 6.54-6.45 (m) and 6.39 (dd)	-H	5.66 (d)	-H	3.66 (ddd)	3.12-2.90 (m)	4.22 (q) and 1.27 (t)

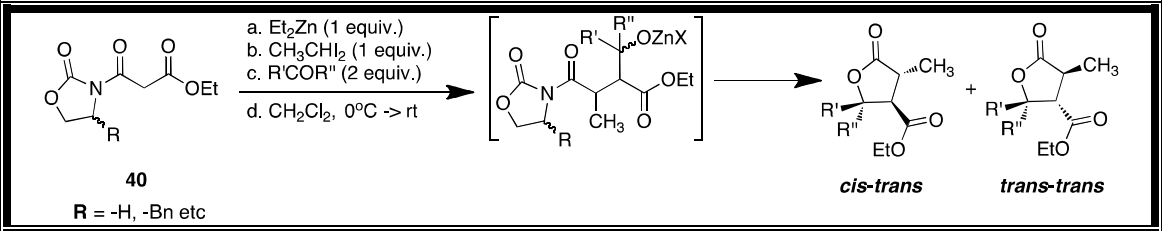
* isolation of *trans* lactone **4a** was unsuccessful
\# isolation of the *cis* lactone **8b** was unsuccessful

Although *trans* lactone (entry **4a**) was not isolated, assignment of the structure was based on literature reported results.[68]

4.5 Future work towards tandem chain extension-aldol reaction and lactonization:

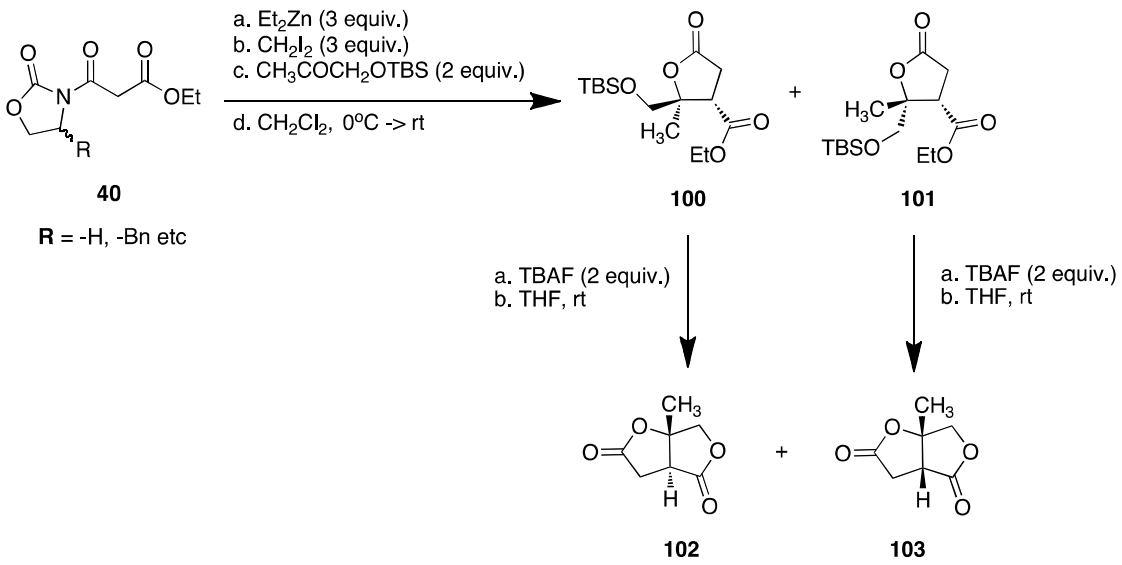
Tandem chain extension aldol and lactonization reaction using simple ketones like acetone has been reported within the Zercher group.[9,15] Sadlowski[15] reported that use of a substituted zinc-carbenoid could be used to alter the diastereoselectivity of the tandem chain extension-aldol reaction and lactonization (**Table 12**). The opportunity to create these contiguous structures within a lactone skeleton in one step is available and continued research in this area is necessary to address the stereochemical issues.

Table 12: Percent yields of α-methylated-γ-substituted lactones using 1,1-diiodoethane



Entry	R	R'	R''	*Cis-Trans* isomer	*Trans-Trans* isomer	Yield %
1.	-H	$-(CH_2)_4-CH_3$	-H	4	3	72
2.	-H	$-C_6H_5$	-H	5	3	78
3.	-H	$-CH_3$	$-CH_3$	3	2	86

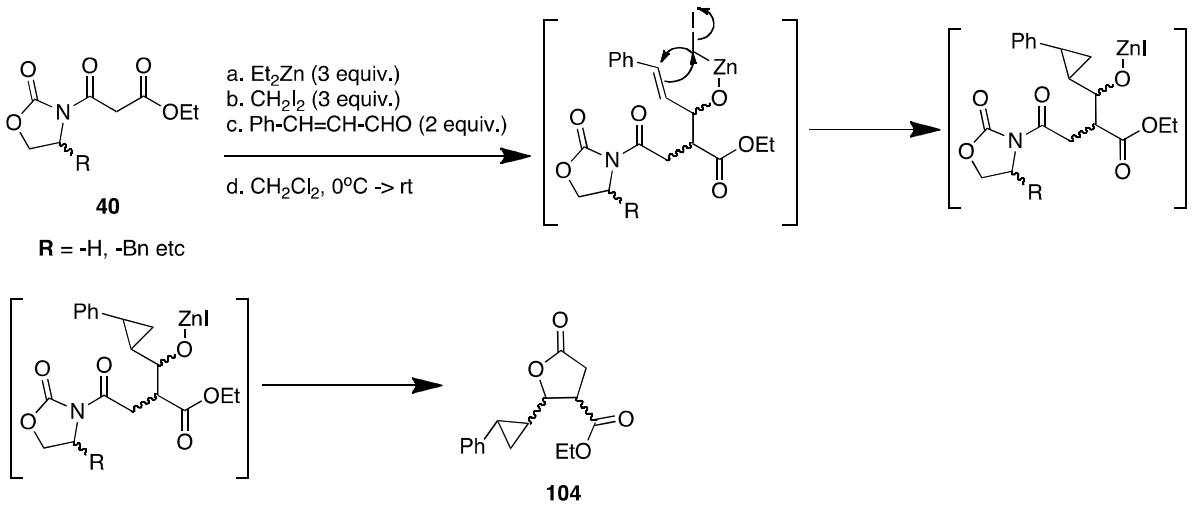
Similar reaction conditions could be employed to trap silylated α-hydroxy ketones followed by lactonization. Deprotection of the TBDMS ether of the diastereomeric lactones **100** and **101** using tetra-n-butylammonium fluoride (TBAF) could result in the formation of diastereomeric β-methylated bis-lactones **102** and **103** (**Scheme 4.9**).



Scheme 4.9: Proposed formation of diastereomeric bis-lactones **102** and **103** from γ-substituted lactones **100** and **101**

Compounds of these type exhibit anti-bacterial and anti-fungal properties.[72] Additional studies on the stereochemical control of such systems could also facilitate the production of several amino sugars and ribonolactones.[73]

Brogan[7] and Zercher pioneered the zinc carbenoid mediated chain-homologation cyclopropanation using a carbenoid that can effect cyclopropanation of olefins. It would be interesting to explore tandem chain extension-aldol reaction and lactonization to make novel cyclopropyl substituted γ-lactones. A proposed synthetic route is described in (**Scheme 4.10**).



Scheme 4.10: Proposed mechanistic route to make cyclopropyl substituted γ-lactones **104** using α-carboxyester imide **40**

Chapter 5

Experimental Section

5.1 General Experimentals:

All reactions were performed in oven-dried glassware and stirred with Teflon-coated magnetic stir bars. The concentration of crude mixtures and products was performed using rotary evaporators (10 mmHg, 30 °C) followed by placement on a high vacuum line (0.5 mmHg, 20 °C) for at least 6 hours unless specified differently.

5.2 Solvents:

Anhydrous solvents were dried and dispensed from an Innovative Technology Inc. Solvent delivery system prior to use. Solvents like dichloromethane (DCM), tetrahydrofuran (THF), N,N-dimethylformamide (DMF), diethyl ether, hexanes and toluene were dried over 4Å molecular sieves. Tetrahydrofuran was dried over 3Å molecular sieves for an additional 48h prior to use. The deuterated solvent for NMR analysis, chloroform-d ($CDCl_3$), was dried over 3Å molecular sieves prior to use.

5.3 Chemicals and Reagents:

Unless otherwise noted, all chemicals and reagents were obtained from commercial sources and were used as received. Moisture sensitive chemicals and reagents, trimethylsilylchloride (TMSCl). Diisopropylamine, and triethyl amine were distilled and dried over 3Å molecular sieves prior to use and stored under inert atmosphere and dark conditions.

5.4 Chromatography:

Flash chromatography was performed using Silica-P flash Silica Gel with 40-63 μm particle size, Solvent systems used for preparing the mobile phase are illustrated in the detailed experimentals. Hexane(s) was always distilled prior to use. Other solvents were used as received from commercial sources. The solvent systems used for the mobile phase were identical to the solvent system composition employed for thin layer chromatographic (TLC) analysis unless otherwise noted. TLC analysis was performed using glass backed TLC plates and visualized under ultra-violet (UV) light, staining with *p*-anisaldeyde, phosphomolybdic acid, potassium permanganate or an iodine chamber.

5.5 Spectroscopy:

Nuclear Magnetic Resonance (NMR) spectroscopy was employed using a Varian *Mercury* spectrometer, which operated at 400 and 500 MHz for ^{1}H and 101 and 126 MHz for ^{13}C analysis, unless otherwise noted. All carbon spectra were proton decoupled and referenced to deuterated chloroform ($CDCl_3$): δ 77.16 ppm. All ^{1}H and ^{13}C NMR analyses were performed using deuterated chloroform ($CDCl_3$): δ 7.24 ppm as the solvent. All ^{1}H and ^{13}C resonances were referenced relative to tetramethylsilane (TMS) [δ 0.00 ppm]. Product ratios within the crude reaction mixture were calculated from integrations obtained by applying a MestReNova line fit simulation in all ^{1}H NMR spectra.

5.6 Detailed Experimental Procedures:

2-(2-Hydroxy-2-methylcyclopropyl)-1-phenylethanone (16) and 1-(2-Hydroxy-2-phenylcyclopropyl)-propan-2-one (18):

A 100-mL round-bottomed flask, equipped with a septum, magnetic stir bar, and a nitrogen inlet, was charged with methylene chloride (100 mL) and cooled in an ice bath. Diethylzinc (2.6 mL, 25.6 mmol) was added to the flask and stirred for 10 min, at which time methylene iodide (4.7 mL, 58.6 mmol) was added drop-wise over 5 min. The reaction was allowed to stir for 10 min followed by the addition of 1-phenylbutane-1,3-dione **4** (0.836 g, 5.16 mmol) in methylene chloride (30 mL). The mixture was allowed to stir for 10 min in an ice-cold water bath and quenched with saturated ammonium chloride (20 mL). The aqueous layer was extracted with methylene chloride (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried with anhydrous magnesium sulfate (*ca.* 5 g), filtered, and concentrated in vacuo to give a yellow viscous oil. After column chromatography, compound **16 (**0.150 g, 16%) (R_f = 0.13, hexane:ethyl acetate, 4:1) and compound **18 (**0.115 g,12%) (R_f = 0.11, hexane:ethyl acetate, 4:1) were isolated as clear yellowish oils. ^{1}H NMR (400 MHz, $CDCl_3$) Major (**16**): δ 8.05–7.92 (m, 2H), 7.57 (m, 1H), 7.51–7.42 (m, 2H), 3.53 (dd, *J* = 17.3, 5.2 Hz, 1H), 2.85 (dd, *J* = 17.3, 8.9 Hz, 1H), 2.54 (s, 1H), 1.50 (s, 3H), 1.00 (tdd, *J* = 9.0, 6.1, 5.2 Hz, 1H), 0.75 (dd, *J* = 9.1, 5.6 Hz, 1H), 0.56 (t, *J* = 5.9 Hz, 1H). ^{1}H NMR (400 MHz, $CDCl_3$) Minor (**18**): δ 7.41–7.28 (m, 4H), 7.23 (m, 1H), 3.03 (dd, *J* = 17.3, 5.2 Hz, 1H), 2.93 (s, 1H), 2.59 (dd, *J* = 17.1, 8.6 Hz, 1H), 2.22 (s, 3H), 1.38 (dt, *J* = 8.6, 6.0 Hz, 1H), 1.31 (m, 1H), 0.94 (t, *J* = 6.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) Major (**16**): δ 201.7, 137.0, 133.4, 128.8, 128.4, 54.8, 38.1, 26.0, 20.7, 20.0. ^{13}C NMR (101 MHz, $CDCl_3$) Minor (**18**): δ 210.3, 144.5, 128.6, 126.9, 125.2, 58.9, 43.1, 30.6, 23.4, 22.5.

1-Phenyl-1, 5-hexanedione (26), 3-Methyl-1-phenyl-1,4-pentanedione (25) and 2-Methyl-1-phenylpentane-1,4-dione (24):

A 100-mL dry and clean round-bottomed flask, equipped with a septum, magnetic stir bar, and a nitrogen inlet, was dispensed with 1-phenylbutane-1,3-dione **14** (0.836 g, 5.16 mmol) under a stream of nitrogen. The reaction flask was charged with methylene chloride (50 mL) and cooled in an ice bath. Diethylzinc (2.64 mL, 25.6 mmol) was added to the flask and stirred for 10 min, at which time methylene iodide (4.72 mL, 58.6 mmol) was added drop-wise over 5-8 min. The reaction mixture was allowed to stir for 20 min in an ice-cold water bath followed by stirring at room temperature for 25 min. The reaction mixture was quenched with saturated ammonium chloride (20 mL). The aqueous layer was extracted with methylene chloride (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried with anhydrous magnesium sulfate (*ca.* 5 g), filtered, and concentrated in vacuo to give a yellow viscous oil. After column chromatography, compound **26 (**0.075 g, 8%) (R_f = 0.18, hexane:ethyl acetate, 4:1) was isolated as a beige to colorless solid (mp = 65-67^{o}C). **18 (**0.086 g, 8%) (R_f = 0.11, hexane:ethyl acetate, 4:1), **16 (**0.115 g, 15%) (R_f = 0.13, hexane:ethyl acetate, 4:1), **25 (**0.092 g, 10%) (R_f = 0.37, hexane:ethyl acetate, 4:1) and **24 (**0.045 g, 5%) (R_f = 0.31, hexane:ethyl acetate, 4:1) were isolated as clear yellowish oils. ^{1}H NMR (400 MHz, $CDCl_3$) (**26)**: δ 8.03–7.93 (m, 2H), 7.62-7.40 (m, 3H), 3.02 (t, *J* = 7.0 Hz, 2H), 2.58 (t, *J* = 7.0 Hz, 2H), 2.16 (s, 3H), 2.02 (p, *J* = 7.1 Hz, 2H). ^{1}H NMR (400 MHz, $CDCl_3$) (**25**): δ 8.03 – 7.89 (m, 2H), 7.61-7.37 (m, 3H), 3.53 (dd, *J* = 3.0, 1.8 Hz, 1H), 3.23 (m, 1H), 2.94 (dd, *J* = 18.0, 4.5 Hz, 1H), 2.30 (s, 3H), 1.20 (d, *J* = 5.5 Hz, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**24**)**:** δ 8.04–7.92 (m, 2H), 7.63-7.41 (m, 3H), 3.98 (ddd, *J* = 8.5, 7.2, 5.0 Hz, 1H), 3.17 (dd, *J* = 18.1, 8.5 Hz, 1H), 2.56 (dd, *J* = 18.1, 5.0 Hz, 1H), 2.18 (s, 3H), 1.19 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (**26**): δ 208.7, 200.0, 137.0, 133.3, 128.8, 128.3, 42.8, 37.6, 30.2, 18.4. ^{13}C NMR (101 MHz, $CDCl_3$) (**25**): δ 211.7, 198.7, 136.8, 133.4, 128.8, 128.2, 42.0, 41.9, 29.0, 17.0. ^{13}C NMR (101 MHz, $CDCl_3$) (**24**): δ 207.4, 203.5,

136.2, 133.2, 128.9, 128.7, 47.1, 36.4, 30.4, 18.0. The presence of Minor (**18**) and Major (**16**) in the crude reaction were confirmed through the presence of the following resonances: ^{1}H NMR (400 MHz, $CDCl_3$) Minor (**18**): δ 7.41–7.28 (m, 4H), 7.23 (m, 1H), 3.03 (dd, *J* = 17.3, 5.2 Hz, 1H), 2.93 (s, 1H), 2.59 (dd, *J* = 17.1, 8.6 Hz, 1H), 2.22 (s, 3H), 1.38 (dt, *J* = 8.6, 6.0 Hz, 1H), 1.31 (m, 1H), 0.94 (t, *J* = 6.0 Hz, 1H). ^{1}H NMR (400 MHz, $CDCl_3$) Major (**16**): δ 8.05–7.92 (m, 2H), 7.57 (m, 1H), 7.51–7.42 (m, 2H), 3.53 (dd, *J* = 17.3, 5.2 Hz, 1H), 2.85 (dd, *J* = 17.3, 8.9 Hz, 1H), 2.54 (s, 1H), 1.50 (s, 3H), 1.00 (tdd, *J* = 9.0, 6.1, 5.2 Hz, 1H), 0.75 (dd, *J* = 9.1, 5.6 Hz, 1H), 0.56 (t, *J* = 5.9 Hz, 1H).

1-Phenylpentane-1,5-dione (29) and regioisomeric cyclopropanols 18 and 16:

A 100-mL round-bottomed flask, equipped with a septum, magnetic stir bar, and a nitrogen inlet, was charged with methylene chloride (100 mL) and cooled in an ice bath. Diethylzinc (2.6 mL, 25.6 mmol) was added to the flask and stirred for 10 min, at which time methylene iodide (4.7 mL, 58.6 mmol) was added drop-wise over 5 min. The reaction was allowed to stir for 10 min followed by the addition of 1-phenylbutane-1,3-dione **14** (0.836 g, 5.16 mmol) in methylene chloride (30 mL). The mixture was allowed to stir for 2 min in an ice-cold water bath and quenched with saturated ammonium chloride (20 mL). The aqueous layer was extracted with methylene chloride (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried with anhydrous magnesium sulfate (*ca.* 5 g), filtered, and concentrated in vacuo to give a yellow viscous oil. After column chromatography **29 (**0.150g, 17%) of (R_f = 0.18, hexane:ethyl acetate, 4:1) was isolated as a clear yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) (**29**): δ 8.06–7.92 (m, 2H), 7.64-7.37 (m, 3H), 3.28 (t, *J* = 6.0 Hz, 2H), 2.89 (t, *J* = 6.0 Hz, 2H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (**29**): δ 207.5, 198.7, 136.8, 133.4, 128.5, 37.3, 32.6, 30.4. The presence of the regioisomeric cyclopropanols **18** and **16** along with the chain extended γ-di

ketone **29** and the β-di ketone **14** in a 1 : 0.5 : 6.5 : 10 ratio within the crude reaction mixture was characterized by the following resonances: ^{1}H NMR (400 MHz, $CDCl_3$) (**14**): 2.20 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**29**): 2.26 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**18**): 2.22 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**16**): 1.50 (s, 3H). The presence of the α, β-methylated-γ-di ketones **24** and **25** along with the chain extended γ-di ketone **29** and the β-di ketone **14** in a 1 : 1 : 6.5 : 10 ratio within the crude reaction mixture was characterized by the following resonances: ^{1}H NMR (400 MHz, $CDCl_3$) (**14**): 2.20 (s, 3H). : ^{1}H NMR (400 MHz, $CDCl_3$) (**29**): ^{1}H NMR (400 MHz, $CDCl_3$) (**29**): 2.26 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**25**): 2.30 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**24**): 2.18 (s, 3H).

Biscarbenoid [$Zn(CH_2I)_2$] rearrangement of regioisomeric cyclopropanol 16 to 18:

A 50-mL dry and clean round-bottomed flask, equipped with a septum, magnetic stir bar, and a nitrogen inlet, was charged with dichloromethane (15 mL). The reaction flask was cooled in an ice-cold water bath and stirred for 5-10 min. Diethyl zinc (0.080 mL, 0.790 mmol) was added to the reaction flask followed by dropwise addition of diiodomethane (0.127 mL, 1.58 mmol). The reaction mixture was stirred for 10 min before it was dispensed with the methyl cyclopropanol **16** (0.030 g, 0.158 mmol) in dichloromethane (3 mL). The contents within the reaction flask were allowed to stir for 0.5 h after which it was quenched with saturated ammonium chloride (10 mL). The aqueous layer was extracted with methylene chloride (2 x 15 mL). The combined organic layers were washed with brine (2 x 15 mL), dried with anhydrous magnesium sulfate (*ca.* 0.8 g), filtered and concentrated in-vacuo to give a yellow viscous oil. The presence of a 1 : 1 mixture of regioisomeric cyclopropanols **16** and **18** within the crude reaction mixture were confirmed through the presence of the following NMR resonances: ^{1}H NMR (400 MHz, $CDCl_3$) (**16**): δ 8.05–7.92 (m, 2H), 7.57 (m, 1H), 7.51–7.42 (m, 2H), 3.53 (dd, J = 17.3, 5.2 Hz, 1H), 2.85

(dd, *J* = 17.3, 8.9 Hz, 1H), 2.54 (s, 1H), 1.50 (s, 3H), 1.00 (tdd, *J* = 9.0, 6.1, 5.2 Hz, 1H), 0.75 (dd, *J* = 9.1, 5.6 Hz, 1H), 0.56 (t, *J* = 5.9 Hz, 1H). ^{1}H NMR (400 MHz, $CDCl_3$) (**18**): δ 7.41–7.28 (m, 4H), 7.23 (m, 1H), 3.03 (dd, *J* = 17.3, 5.2 Hz, 1H), 2.93 (s, 1H), 2.59 (dd, *J* = 17.1, 8.6 Hz, 1H), 2.22 (s, 3H), 1.38 (dt, *J* = 8.6, 6.0 Hz, 1H), 1.31 (m, 1H), 0.94 (t, *J* = 6.0 Hz, 1H).

Diethylzinc (Et_2Zn) rearrangement of regioisomeric cyclopropanol 18 to 16 and formation of α, β-methylated-γ-diketones 24, 25 and the δ-diketone 26:

A 100-mL dry and clean round-bottomed flask, equipped with a septum, magnetic stir bar, and a nitrogen inlet, was charged with dichloromethane (30 mL). The reaction flask was cooled in an ice-cold water bath and stirred for 5 min before it was dispensed with the aryl cyclopropanol **18** (0.058 g, 0.308 mmol) in dichloromethane (4 mL). Diethylzinc (0.032 mL, 0.308 mmol) was added to the flask and the reaction mixture was allowed to stir for 13 h after which it was quenched with saturated ammonium chloride (20 mL). The aqueous layer was extracted with methylene chloride (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried with anhydrous magnesium sulfate (*ca.* 0.8 g), filtered, and concentrated in vacuo to give a yellow viscous oil. The presence of the regioisomeric cyclopropanols **16** and **18** along with the chain extended δ-di ketone **26** in a 2 : 1 : 1 ratio within the crude reaction mixture was confirmed through the presence of the following NMR resonances: ^{1}H NMR (400 MHz, $CDCl_3$) Major (**16**): 1.50 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**18)**: 2.22 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**26**): 2.16 (s, 3H). The presence of the regioisomeric cyclopropanols **16** and **18** along with the α,β-methylated-γ-di ketones **24** and **25** in a 2 : 1 : 0.3 : 0.2 mixture in the crude reaction mixture was characterized by the following resonances: :^{1}H NMR (400 MHz, $CDCl_3$) (**16**): 1.50 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**18)**: 2.22 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**25**): 2.30 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**24**): 2.18 (s, 3H).

Diethylzinc (Et_2Zn) rearrangement of regioisomeric cyclopropanol 18 to 16 in presence of diiodozinc (ZnI_2) and formation of α, β-methylated-γ-diketones 24, 25 and the δ-diketone 26:

A 100-mL dry and clean round-bottomed flask, equipped with a magnetic stir bar, molecular iodine (I_2) (0.178 g, 0.352 mmol) was dispensed under a stream of nitrogen and capped with a septum. The flask equipped with a nitrogen intlet was then charged with dichloromethane (30 mL). The reaction flask was cooled in an ice-cold water batch and stirred for 5 min. Diethylzinc (0.036 mL, 0.352 mmol) was added dropwise to the reaction flask and the reaction mixture was allowed to stir at room temperature for 10 minutes. The reaction mixture was cooled down to 0 – 2^oC at which time the aryl cyclopropanol 18 (0.067 g, 0.352 mmol) was added to the reaction flask and the contents were allowed to stir at room temperature for 12.5 h. The reaction mixture was quenched with saturated ammonium chloride (20 mL). The aqueous layer was extracted with methylene chloride (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried with anhydrous magnesium sulfate (*ca.* 0.8 g), filtered, and concentrated in vacuo to give a yellow viscous oil. The formation of the methyl cyclopropanol **16** along with the α-methylated-γ-di ketone **25** and the chain extended δ-di ketone **26** in a 0.4 : 0.6 : 1 ratio within the crude reaction mixture was determined by the following NMR resonances: ^1H NMR (400 MHz, $CDCl_3$) (**16**): 1.50 (s, 3H). ^1H NMR (400 MHz, $CDCl_3$) (**25**): 2.30 (s, 3H). ^1H NMR (400 MHz, $CDCl_3$) (**26**): 2.16 (s, 3H). The presence of the aryl cyclopropanol 18 along with the β-methylated-γ-di ketone in a 0.5 : 0.2 ratio within the crude reaction mixture was determined by the following NMR resonances: ^1H NMR (400 MHz, $CDCl_3$) (**18)**: 2.22 (s, 3H). ^1H NMR (400 MHz, $CDCl_3$) (**24**): 2.18 (s, 3H).

Sodium Hydride (NaH) rearrangement of the regioisomeric cyclopropanol 18 to 16 and formation of α-methylated-γ-diketone 25 and the δ-diketone 26:

A dry 100 mL round bottom flask was equipped with Nitrogen inlet to which sodium hydride (0.0158 g, 0.658 mmol) (60% mineral oil) was transferred and washed with (4 x 5 mL) of distilled hexanes. The supernatant was slowly removed by cannulation and the process was repeated three times with 5mL portions of hexanes (3 x 5 mL). The residual sodium hydride was dried under nitrogen for 5 h and weighed (0.0108 g, 0.305 mmol) until it was dissolved in anhydrous tetrahydrofuran (30 mL). This was then cooled in an ice-bath and allowed to stir for 5 min. before aryl cyclopropanol **18** (0.0462 g, 0.244 mmol) in tetrahydrofuran (4 mL) was added and the reaction mixture was allowed to stir at room temperature for 12.5 h. Saturated ammonium chloride (20 mL) was added to quench the reaction mixture. The reaction mixture was concentrated in vacuo to remove excess tetrahydrofuran. The aqueous layer was extracted with (2 x 15 mL) of methylene chloride. The combined organic layers were washed with brine (2 x 15 mL), dried with anhydrous magnesium sulfate (*ca.* 0.8 g), filtered, and concentrated in vacuo to give a yellow viscous oil. The presence of the regioisomeric cyclopropanols **18** and **16** along with the chain extended δ-di ketone **26** in a 1 : 0.6 : 0.4 ratio within the crude reaction mixture was confirmed through the presence of the following NMR resonances: ^{1}H NMR (400 MHz, $CDCl_3$) (**16**): 1.50 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**18)**: 2.22 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**26**): 2.16 (s, 3H). The presence of The presence of the regioisomeric cyclopropanols **18** and **16** along with the α-methylated-γ-di ketone 25 in a 1 : 0.4 : 0.2 ratio within the crude reaction mixture was characterized by the following NMR resonances: ^{1}H NMR (400 MHz, $CDCl_3$) (**16**): 1.50 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**18)**: 2.22 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**25**): 2.30 (s, 3H).

Potassium *tert*- Butoxide (t-BuO$^-$K$^+$) rearrangement of 18 to 16 and formation of 3-Hydroxy-3-phenyl-cyclohexanone (27) and 3-phenyl-2-Cyclohexen-1-one (28), 24, 25 and 26:

A dry and clean 100-mL round-bottomed flask equipped with a septum, a magnetic stir bar and a nitrogen inlet was charged with tetrahydrofuran (30 mL) and cooled in an ice bath to which potassium t-butoxide (0.044 g, 0.394 mmol) was added. The septum was replaced and the flask was flushed with nitrogen. The solution was then allowed to stir for 5 min before aryl cyclopropanol **18** (0.075g, 0.394 mmol) in tetrahydrofuran (4 mL) was added by syringe. The reaction mixture was allowed to stir at room temperature for 12.5 h. Saturated ammonium chloride (20 mL) was added to quench the reaction mixture. The reaction mixture was concentrated in vacuo to remove excess tetrahydrofuran. The aqueous layer was extracted with (2 x 15 mL) of methylene chloride. The combined organic layers were washed with brine (2 x 15 mL), dried with anhydrous magnesium sulfate (*ca.* 1 g), filtered, and concentrated in vacuo to give a yellow viscous oil. After column chromatography **27 (**0.013 g, 18%) of (R_f = 0.11, hexane:ethyl acetate, 4:1) was isolated as a colorless to white solid (mp = 153-155^{o}C) and 0.021 g (30%) of **28** was isolated as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) (**27**): δ 7.52 – 7.44 (m, 2H), 7.43 – 7.34 (m, 2H), 7.34 – 7.24 (m, 1H), 2.94 (d, *J* = 14.3 Hz, 1H), 2.60 (dt, *J* = 14.3, 2.2, 2.2 Hz, 1H), 2.54 – 2.30 (m, 2H), 2.29 – 2.13 (m, 2H), 2.12 – 1.87 (m, 2H), 1.80 (s, 1H). ^{1}H NMR (400 MHz, $CDCl_3$) (**28**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.48 (m, 2H), 7.48 – 7.35 (m, 3H), 6.43 (s, 1H), 2.78 (t, *J* = 6.1 Hz, 2H), 2.51 (t, *J* = 6.7 Hz, 2H), 2.16 (p, *J* = 12.4, 6.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) (**27**): δ 209.9, 146.9, 128.9, 127.8, 124.6, 78.2, 54.7, 40.9, 38.1, 21.7. ^{13}C NMR (101 MHz, $CDCl_3$) (**28**): ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 160.0, 139.0, 130.2, 129.0, 126.3, 125.7, 37.5, 28.3, 23.1. ^{1}H-COSY experiments on **27** were also

carried out which confirmed the structure assignments. The presence of the regioisomeric cyclopropanols **18** and **16** along with the α-methylated-γ-di ketone **25** and the chain extended δ-di ketone in a 1 : 0.3 : 1 : 1 ratio in the crude reaction mixture were ascertained by the presence of the following NMR resonances: ^{1}H NMR (400 MHz, $CDCl_3$) Major (**16**): 1.50 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**18)**: 2.22 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**25**): 2.30 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**26**): 2.16 (s, 3H). The presence of the regioisomeric cyclopropanols **18** and **16** along with β-methylated-γ-di ketone **24** in a 1 : 0.3 : 0.3 mixture was characterized by the following resonances: ^{1}H NMR (400 MHz, $CDCl_3$) (**16**): 1.50 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**18)**: 2.22 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**24**): 2.18 (s, 3H).

Lithium diisopropylamide rearrangement (LDA) rearrangement of the regioisomeric cyclopropanol 18 to 16 and formation of α, β-methylated-γ-diketones 24, 25 and the δ-diketone 26:

A 100-mL round-bottomed flask equipped with a septum, a magnetic stir bar and a Nitrogen inlet was charged with tetrahydrofuran (30 mL) and cooled in an ice bath to which distilled diisopropylamine (0.062 mL, 0.442 mmol) was added followed by simultaneous and slow addition of n-butyllithium (2.2 M in hexanes) of (0.20 mL, 0.442 mmol). The contents were stirred in an ice-cold water bath for 10 min to generate LDA, which was followed by the addition of the aryl cyclopropanol **18** (0.084 g, 0.442 mmol). The reaction mixture was stirred at room temperature for 12.5 h. Saturated ammonium chloride (20 mL) was added to quench the reaction mixture. The reaction mixture was concentrated in vacuo to remove excess tetrahydrofuran. The aqueous layer was extracted with (2 x 15 mL) of methylene chloride. The combined organic layers were washed with brine (2 x 15 mL), dried with anhydrous magnesium sulfate (*ca.* 2 g), filtered, and concentrated in vacuo to give a yellow viscous oil. The presence of the

regioisomeric cyclopropanols **18** and **16** along with the α-methylated-γ-di ketone **25** and the chain extended δ-di ketone in a 1 : 0.5 : 0.5 : 0.5 ratio in the crude reaction mixture were ascertained by the presence of the following NMR resonances: ^{1}H NMR (400 MHz, $CDCl_3$) (**16**): 1.50 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**18)**: 2.22 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**25**): 2.30 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**26**): 2.16 (s, 3H). The presence of the regioisomeric cyclopropanols **18** and **16** along with β-methylated-γ-di ketone **24** in a 1 : 0.5 : 0.3 mixture was characterized by the following resonances: ^{1}H NMR (400 MHz, $CDCl_3$) Major (**16**): 1.50 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**18)**: 2.22 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**24**): 2.18 (s, 3H).

DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) rearrangement of the regioisomeric cyclopropanol 18 to 16 and formation of α, β-methylated-γ-diketones 24 and 25:

To a dry and clean 100-mL round-bottomed flask equipped with a magnetic stir bar, diiodozinc (ZnI_2) (0.118 g, 0.371 mmol) was dispensed under a stream of nitrogen and placed in the oven maintained between 300 - 450^{o}C for about 6 h. The reaction flask was cooled under a flow of nitrogen, sealed with a septum and then charged with dichloromethane (40 mL) and cooled in an ice-bath to which the aryl cyclopropanol **18** (0.088 g, 0.463 mmol) dissolved in dichloromethane (2 mL) was dispensed. The reaction flask was then allowed to stir for 5 min before DBU (0.069 mL, 0.463 mmol) was added. The reaction mixture was allowed to stir at room temperature for 12 h. At this time saturated ammonium chloride (20 mL) was added to the reaction mixture. The aqueous layer was extracted with (2 x 20 mL) of methylene chloride, the combined organic layers were washed with brine (2 x 20 mL), dried with anhydrous magnesium sulfate (*ca.* 2 g), filtered, and concentrated in vacuo to give a yellow viscous oil. Compound **16** was not present in the crude reaction mixture, however its formation was supported by the

presence of **25**, which is presumed to be formed by the fragmentation of **16** under the influence of the Lewis acid catalyst. The formation of a 1 : 1 : 0.4 mixture of the aryl cyclopropanol **18** along with the α, β-methylated-γ-di ketones **24** and **25** in the crude reaction mixture was determined by the presence of the following NMR resonances: ^{1}H NMR (400 MHz, $CDCl_3$) (**18)**: 2.22 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**24**): 2.18 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**25**): 2.30 (s, 3H).

Di-n-butylmagnesium [$(C_4H_9)_2Mg$] rearrangement of the regioisomeric cyclopropanol 18 to 16 and formation of the β-methylated-γ-diketone 24 and the δ-diketone 26:

A dry and clean 100-mL round-bottomed flask equipped with a septum, a magnetic stir bar and a nitrogen inlet was charged with dichloromethane (20 mL) and cooled in an ice bath to which aryl cyclopropanol **18** (0.042 g, 0.224 mmol) dissolved in of dichloromethane was added (2 mL). The solution was then allowed to stir for 5 min. Di-n-butyl magnesium (1.0 M in heptane) 0.035 mL (0.112 mmol) was then added and the reaction mixture was allowed to stir at room temperature for 3.5 h. Saturated ammonium chloride (20 mL) was added to quench the reaction mixture. The aqueous layer was extracted with (2 x 15 mL) of dichloromethane, the combined organic layers were washed with brine (2 x 15 mL), dried with anhydrous magnesium sulfate (*ca.* 1 g), filtered, and concentrated in vacuo to give a yellow viscous oil. The formation of a 1 : 0.3 : 0.5 : 0.5 mixture of the regioisomeric cyclopropanols **18** and **16** along with the β-methylated-γ-diketone **24** and the chian extended δ-di ketone was determined by the presence of the following resonances: ^{1}H NMR (400 MHz, $CDCl_3$) (**16**): 1.50 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**18)**: 2.22 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**24**): 2.18 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**26**): 2.16 (s, 3H).

1-(2-((*tert*-Butyldimethylsilyl)oxy)-2-phenylcyclopropyl)propan-2-one (35):

To an oven-dried and clean 100-mL round-bottomed flask, tertiary butyl dimethyl silyl chloride (TBDMSCl) (0.033 g, 0.225 mmol) and Imidazole (0.010 g, 0.230 mmol) were dispensed under a stream of nitrogen. The reaction flask was then equipped with a septum, a magnetic stir bar and a nitrogen inlet. The reaction flask was then charged with dimethyl formamide (DMF) (25 mL) and the contents were stirred in an ice-cold water bath. This was followed by the simultaneous addition of the regioisomeric aryl cyclopropanol **18** (0.042 g, 0.225 mmol) dissolved in dichloromethane (2 mL). The reaction mixture was then allowed to stir at room temperature for 4-5 h. Saturated ammonium chloride (20 mL) was added to quench the reaction mixture. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried with anhydrous magnesium sulfate (*ca.* 1 g), filtered, and concentrated in vacuo to give a yellow viscous oil. After column chromatography **35 (**0.018 g, 49%) (R_f = 0.42, hexane:ethyl acetate, 4:1) was isolated as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) (**35**): δ 7.68 – 7.37 (m, 5H), 2.93 (dddd, *J* = 17.0, 17.0, 8.0, 8.0 Hz, 2H), 2.45 (s, 3H), 1.82 (dd, *J* = 10.0, 6.0 Hz, 1H), 1.42 – 1.24 (m, 1H), 1.09 (s, 9H), 0.97 (t, *J* = 6.5 Hz, 1H), 0.24 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) (**35**): δ 212.7, 147.6, 131.8, 130.6, 130.4, 64.1, 46.6, 33.4, 29.6, 26.5, 22.2, 21.8, 4.79.

Zinc triflate mediated [$Zn(OTf)_2$] deprotection of 35 and rearrangement of the regioisomeric cyclopropanol 18 to 16:

To a dry and clean 100-mL round-bottomed flask equipped with a magnetic stir bar, zinc trifluoromethane sulfonate [$Zn(OTf)_2$] (0.038 g, 0.105 mmol) was dispensed under a stream of nitrogen and placed in the oven maintained between 300 - 450 ^{o}C for about 3.0 h. The reaction flask was then purged with nitrogen and charged with dichloromethane (30 mL) and the flask

was cooled in an ice-bath. At this time TBDMS ether of the aryl cyclopropanol **35** (0.032 g, 0.105 mmol) dissolved in dichloromethane (4 mL) was added to the flask by syringe. The reaction mixture was then allowed to stir for 20 min at 0 - 2 ^{o}C followed by stirring at room temperature for 35 min. At this time saturated ammonium chloride (20 mL) was added to the reaction mixture. The aqueous layer was extracted with dichloromethane (2 x 15 mL). The combined organic layers were washed with brine (2 x 15 mL), dried with anhydrous magnesium sulfate (*ca.* 1 g), filtered, and concentrated in vacuo to give a yellow viscous oil. Use of stoichiometric amounts of zinc triflate resulted in the formation of a 1 : 1 mixture of **18** and **16** in the crude reaction mixture. This was determined by the following NMR resonances: ^{1}H NMR (400 MHz, $CDCl_3$) (**16**): 1.50 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**18)**: 2.22 (s, 3H). However catalytic amounts of zinc triflate (0.020 g, 0.0525 mmol) resulted in a 1 : 0.5 : 0.5 mixture of the regioisomeric cyclopropanols **18** and **16** along with the unreacted starting material **35**. This was characterized by the following NMR resonances: ^{1}H NMR (400 MHz, $CDCl_3$) (**16**): 1.50 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**18)**: 2.22 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**35**): 1.09 (s, 9H), 0.24 (s, 3H).

Tetra-n-butyl ammonium fluoride (TBAF) mediated deprotection of 35 and rearrangement of the regioisomeric cyclopropanol 18 to 16 and formation of β-methylated-γ-diketone 24, δ-diketone 26, ketol 27 and enone 28:

An oven-dried 25 mL round bottom flask equipped with a magnetic stir bar and a nitrogen gas inlet was charged with anhydrous tetrahydrofuran (250 mL) and cooled to 0-2^{o}C in an ice-cold water bath. TBDMS protected aryl cyclopropanol 35 (0.0247g, 0.082 mmol) dissolved in tetrahydrofuran (2 mL) was added to the reaction flask followed by simultaneous addition of tetra-n-butyl ammonium fluoride (1M in THF) (0.024 mL, 0.082 mmol). The reaction mixture

was initially allowed to stir for 0.5 h followed by an overnight stir at room temperature for 16 h. At this time saturated ammonium chloride (5 mL) was added to the reaction mixture. Excess tetrahydrofuran was concentrated in vacuo and the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic layers were washed with brine (2 x 5 mL), dried with anhydrous magnesium sulfate (*ca.* 0.5 g), filtered, and concentrated in vacuo to give a reddish-brown oil. After column chromatography of the 12 h crude reaction mixture (Hexane:Ethyl acetate, 2:1), the formation of 0.7 : 1 : 0.5 mixture of the methyl cyclopropanol **16**, β-methylated-γ-diketone **24** and the chain extended δ-diketone **26** within the mixture (i.e. a yellowish oil) was ascertained by the presence of the following NMR resonances: ^{1}H NMR (400 MHz, $CDCl_3$) (**16**): 1.50 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**24**): 2.18 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**26**): 2.16 (s, 3H). However after column chromatography of the 16 h crude reaction mixture (Hexane:Ethyl acetate, 2:1), the formation of a 1 : 1 : 1 mixture of the chain extended δ-di ketone **26**, the ketol **27** and the enone **28** within the crude mixture (i.e. yellow to off-white solid) was ascertained by the presence of the following NMR resonances: ^{1}H NMR (400 MHz, $CDCl_3$) (**26**): 2.16 (s, 3H), 3.02 (t, J = 7.0 Hz, 2H), 2.58 (t, J = 7.0 Hz, 2H), 2.02 (p, J = 7.1 Hz, 2H). ^{1}H NMR (400 MHz, $CDCl_3$) (**27**): 2.94 (d, J = 14.3 Hz, 1H), 2.60 (dt, J = 14.3, 2.2, 2.2 Hz, 1H), 2.54 – 2.30 (m, 2H), 2.29 – 2.13 (m, 2H), 2.12 – 1.87 (m, 2H), 1.80 (s, 1H). ^{1}H NMR (400 MHz, $CDCl_3$) (**28**): 6.43 (s, 1H), 2.78 (t, J = 6.1 Hz, 2H), 2.51 (t, J = 6.7 Hz, 2H), 2.16 (p, J = 12.4, 6.2 Hz, 2H).

Ethyl 3-oxo-3-(2-oxooxazolidin-3-yl)propanoate (40):

A 100 mL oven-dried round-bottomed flask, equipped with a septum, nitrogen gas inlet and a magnetic stir bar was charged with the 2-Oxazolidinone (0.661 g, 3.3 mmol) and 4-dimethylamino pyridine (0.092, 0.75 mmol). The contents were dissolved in dichloromethane

(20 mL). The reaction flask was cooled in an ice-cold water bath and magnetically stirred to which triethylamine (1.57 mL, 11.3 mmol) was added. The reaction mixture was allowed to stir at room temperature for 0.5 h and cooled to 0-2 ^{o}C at which time ethyl malonyl chloride (1.5 mL, 12.0 mmol) was added. The reaction mixture was allowed to stir for 1 h and quenched with 1N hydrochloric acid (10 mL). The organic layer was extracted with dichloromethane (2 x 20 mL) and washed initially with sodium bicarbonate (2 x 15 mL) followed by a brine wash (2 x 20 mL). The combined organic layers were dried using anhydrous magnesium sulfate (*ca.* 1 g) and concentrated in-vacuo to yield the crude reaction mixture as a dark-yellowish oil. After column chromatography, α-carboxyester imide **40** (0.450g, 45% yield) (R_f = 0.25, hexane:ethyl acetate, 2:1) was isolated as a colorless to light yellow solid (mp = 75-77 °C). ^{1}H NMR (400 MHz, $CDCl_3$) (**40**): δ 4.46 (t, *J* = 8.0, 8.0 Hz, 2H), 4.21 (q, *J* = 7.1, 7.1, 7.1 Hz, 2H), 4.08 (t, *J* = 7.7, 7.7 Hz, 2H), 3.96 (s, 2H), 1.28 (t, *J* = 7.1, 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (**40**): δ 167.0, 166.1, 153.7, 62.5, 61.9, 42.8, 42.5, 14.3.

Ethyl 2-methyl-3-oxo-3-(2-oxooxazolidin-3-yl)propanoate (98, R = -H) and Ethyl 4-oxo-4-(2-oxooxazolidin-3-yl)butanoate (99, R = -H):

A 50 mL oven-dried round-bottomed flask equipped with a septum, a magnetic stir bar and a nitrogen gas inlet was charged with dichloromethane (20 mL) and magnetically stirred in an ice-cold water bath for 5-10 min. To this diethyl zinc (0.169 mL, 1.64 mmol) was added followed by dropwise addition of diiodomethane (0.132 mL, 1.64 mmol). The reaction mixture was stirred for 10-12 min followed by the rapid addition of the α-carboxyester imide **40 (R = -H)** (0.110 g, 0.546 mmol) in dichloromethane (3 mL). The reaction mixture was allowed to stir at room temperature for 5 h and quenched using saturated ammonium chloride (15 mL). The crude reaction mixture was extracted with dichloromethane (2 x 15 mL) and the organic layers were

washed with brine (2 x 15 mL). The combined organic layers were dried using anhydrous magnesium sulfate (*ca.* 2 g) and concentrated in vacuo to obtain a yellow viscous oil. After column chromatography **99 (R = -H) (**0.018 g, 16%) (R_f = 0.23, hexane:ethyl acetate, 2:1) was isolated as a pale yellowish oil and **98 (R = -H)** (0.035 g, 29% yield) (R_f = 0.25, hexane:ethyl acetate, 2:1) was isolated as a pale yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) (**99, R = -H**): δ 4.43 (t, *J* = 8.2, 8.2 Hz, 2H), 4.16 (q, *J* = 7.2, 7.1, 7.1 Hz, 2H), 4.03 (t, *J* = 8.1, 8.1 Hz, 2H), 3.24 (t, *J* = 6.4, 6.4 Hz, 2H), 2.67 (t, *J* = 6.4, 6.4 Hz, 2H), 1.27 (t, *J* = 7.2, 7.2 Hz, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**98, R = -H**): δ 4.57 – 4.37 (m, 3H), 4.19 (q, *J* = 7.1, 7.1, 7.1 Hz, 2H), 4.08 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 2H), 1.47 (d, *J* = 7.3 Hz, 3H), 1.26 (t, *J* = 7.0, 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) (**99, R = -H**): δ 172.5, 172.1, 153.5, 62.2, 60.7, 42.5, 30.4, 28.4, 14.2. ^{13}C NMR (126 MHz, $CDCl_3$) (**98, R = -H**): δ 170.4, 169.8, 153.5, 62.2, 61.5, 45.5, 42.6, 14.1, 13.2.

(*S*)-2-amino-3-phenylpropan-1-ol (60):

An oven-dried 500 mL three-necked round bottom flask equipped with a magnetic stir bar, water condenser and a nitrogen gas inlet was charged with anhydrous tetrahydrofuran (250 mL) and cooled to 0-2 ^{o}C in an ice-cold water bath. Lithium aluminum hydride (2.29 g, 60.2 mmol) was added in portions to the flask with constant stirring followed by a slow addition of (*S*)-Phenylalanine (5.00 g, 30.2 mmol). The reaction mixture was allowed to stir at room temperature for 0.5 h followed by heating to reflux for 3 h. The reaction mixture was cooled to room temperature. The excess lithium aluminum hydride was quenched with slow addition of 1N sodium hydroxide (20 mL). After the addition of aqueous sodium hydroxide The reaction mixture was again heated to reflux for 1 h. The reaction mixture was cooled to room temperature and vacuum filtered. The aluminum salts within the flask were washed with boiling tetrahydrofuran (2 x 50 mL) and the mixture was vacuum filtered again. The combined organic

layer was dried using anhydrous magnesium sulfate, filtered, concentrated in vacuo to yield the (*S*)-Amino alcohol as a light yellow colored solid (4.12 g, 89% yield). The product was carried on without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) (**60**): δ 7.44 – 7.05 (m, 5H), 3.64 (dd, *J* = 10.6, 3.8 Hz, 1H), 3.38 (dd, *J* = 10.5, 7.2 Hz, 1H), 3.12 (tt, *J* = 8.8, 8.8, 4.7, 4.7 Hz, 1H), 2.80 (dd, *J* = 13.5, 5.2 Hz, 1H), 2.53 (dd, *J* = 13.4, 8.6 Hz, 1H), 1.63 (bs, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) (**60**): δ 138.88, 129.4, 128.8, 126.6, 66.6, 54.4, 41.2.

(*S*)-ethyl (1-hydroxy-3-phenylpropan-2-yl)carbamate (61):

An oven-dried 250 mL round bottomed flask equipped with a magnetic stir bar was charged with the (*S*)-Amino alcohol **60** (4.12 g, 27.3 mmol) was dissolved in a 1 : 1 mixture of tetrahydrofuran (THF) (50 mL) and water (50 mL). Sodium bicarbonate (11.46 g, 136.5 mmol) was added and reaction mixture was magnetically stirred in an ice-cold water bath. Ethylchloroformate (2.86 mL, 30.0 mmol) was added and the reaction mixture was allowed at room temperature for 5 h and then extracted with ethyl acetate (2 x 40 mL). The combined organic extracts were washed with brine (2 x 40 mL) and dried over anhydrous magnesium sulfate (*ca.* 2 g), filtered and concentrated in vacuo to yield the ethyl carbamate **61** as a light yellow solid (4.35 g, 94% yield). The product was carried on without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) (**61**): δ 7.44 – 7.08 (m, 5H), 4.85 (bs, 1H), 4.09 (q, 2H), 3.93 (bs, 1H), 3.64 (ddt, *J* = 44.9, 10.8, 5.2, 5.2 Hz, 1H), 3.02 – 2.68 (m, 3H), 1.22 (t, *J* = 7.1, 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (**61**): δ 157.2, 137.8, 129.5, 128.9, 126.9, 64.5, 61.3, 54.2, 37.6, 14.8.

(R)-4-benzyloxazolidin-2-one (55):

An oven dried 100 mL round-bottomed flask was equipped with a magnetic stir bar and a short path distillation head. The flask was charged with ethyl carbamate (4.35 g, 19.5 mmol) and

potassium carbonate (0.125 g, 0.9 mmol). The reaction was heated to 125-135 ^{o}C under reduced pressure (ca. 40 mmHg) until gas evolution was ceased. The reaction mixture was allowed to cool to room temperature to afford a brown oily solid. The crude product was recrystallized from (2 : 1; Hexanes : Ethyl acetate) to yield the chiral oxazolidinone as a beige colored solid (2.70 g, 97.4% yield). ^{1}H NMR (400 MHz, $CDCl_3$) (**55**): δ 7.41 – 7.23 (m, 3H), 7.23 – 7.13 (m, 2H), 5.03 (bs, 1H), 4.49 (dd, *J* = 8.3, 8.3 Hz, 1H), 4.17 (dd, *J* = 8.6, 5.6 Hz, 1H), 4.09 (ddd, *J* = 13.9, 8.0, 5.8 Hz, 1H), 3.03 – 2.75 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) (**55**): δ 159.7, 136.2, 129.2, 127.5, 69.9, 54.0, 41.8.

(R)-ethyl 3-(4-benzyl-2-oxooxazolidin-3-yl)-3-oxopropanoate (54):

A 50 mL oven-dried round-bottomed flask, equipped with a septum, nitrogen gas inlet and a magnetic stir bar was charged with the chiral oxazolidinone **55** (0.182 g, 1.0 mmol) and 4-dimethylamino pyridine (12 mg, 0.1 mmol). The contents were dissolved in dichloromethane (10 mL). The reaction flask was cooled in an ice-cold water bath and magnetically stirred to which triethylamine (0.280 mL, 1.8 mmol) was added followed by subsequent drop wise addition of ethyl malonyl chloride (0.400 mL, 3.0 mmol). The reaction mixture was allowed to stir overnight and quenched with 1N hydrochloric acid (10 mL). The organic layer was extracted with dichloromethane (2 x 10 mL) and washed initially with saturated sodium bicarbonate (2 x 10 mL) followed by a brine wash (2 x 10 mL). The combined organic layers were dried using anhydrous magnesium sulfate (*ca.* 1 g) and concentrated in-vacuo to yield the crude reaction mixture as a dark-yellowish oil. After column chromatography, α-carboxyester imide **54** (R_f = 0.25, hexane:ethyl acetate, 2:1) was isolated as a colorless oil (0.095g, 36% yield). ^{1}H NMR (400 MHz, $CDCl_3$) (**54**): δ 7.39 – 7.27 (m, 3H), 7.26 – 7.20 (m, 2H), 4.79 – 4.65 (m, 1H), 4.32 – 4.14 (m, 4H), 4.07 – 3.89 (m, 2H), 3.39 (dd, *J* = 13.5, 3.3 Hz, 1H), 2.79 (dd, *J* = 13.4, 9.8 Hz, 1H),

1.30 (t, *J* = 7.1, 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (**54**): δ 166.6, 166.0, 135.3, 129.7, 129.2, 127.6, 66.6, 61.9, 55.4, 43.2, 37.8, 14.3.

(R)-ethyl 4-(4-benzyl-2-oxooxazolidin-3-yl)-4-oxobutanoate (57) and ethyl 3-((R)-4-benzyl-2-oxooxazolidin-3-yl)-2-methyl-3-oxopropanoate (58):

A 50 mL oven-dried round-bottomed flask equipped with a septum, a magnetic stir bar and a nitrogen gas inlet was charged with dichloromethane (20 mL) and magnetically stirred in an ice-cold water bath for 5-10 min. To this diethyl zinc (0.079 mL, 0.771 mmol) was added followed by dropwise addition of diiodomethane (0.062 mL, 0.771 mmol). The reaction mixture was stirred for 10-12 min followed by the rapid addition of the α-carboxyester imide **54** (0.075 g, 0.257 mmol) in dichloromethane (3 mL). The reaction mixture was allowed to stir at room temperature for 5 h and quenched using saturated ammonium chloride (15 mL). The crude reaction mixture was extracted with dichloromethane (2 x 15 mL) and the organic layers were washed with brine (2 x 15 mL). The combined organic layers were dried using anhydrous magnesium sulfate (*ca.* 2 g) and concentrated in vacuo to obtain a yellow viscous oil. After column chromatography **57 (**0.025 g, 32%) (R_f = 0.36, hexane:ethyl acetate, 2:1) was isolated as a pale yellowish oil and **58** (0.015 g, 19% yield) (R_f = 0.38, hexane:ethyl acetate, 2:1) was isolated as a pale yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) (**57**): δ 7.46 – 7.12 (m, 4H), 4.68 (ddt, *J* = 10.4, 7.0, 3.1, 3.1 Hz, 1H), 4.37 – 4.03 (m, 3H), 3.44 – 3.12 (m, 2H), 2.96 – 2.52 (m, 2H), 1.32 (t, *J* = 7.0, 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (**57**): δ 172.7, 153.7, 135.4, 129.7, 129.2, 127.6, 66.6, 61.0, 55.4, 38.0, 31.1, 28.6, 14.4. ^{1}H NMR (400 MHz, $CDCl_3$) (**58**): δ 7.43 – 7.24 (m, 4H), 4.69 (ddd, *J* = 10.1, 6.7, 3.5 Hz, 1H), 4.51 (q, *J* = 7.2, 7.2, 7.2 Hz, 1H), 4.26 – 4.16 (m, 4H), 3.42 (dd, *J* = 13.5, 3.2 Hz, 1H), 2.76 (dd, *J* = 13.5, 10.0 Hz, 1H), 1.49 (d, *J* = 7.2

Hz, 3H), 1.29 (t, *J* = 7.1, 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (**58**): δ 172.7, 154.7, 135.4, 129.5, 129.0, 127.4, 66.3, 61.5, 55.5, 45.7, 37.4, 14.1, 13.2.

(2S,3R)-ethyl 5-oxo-2-phenyltetrahydrofuran-3-carboxylate (1a) and (2R,3R)-ethyl 5-oxo-2-phenyltetrahydrofuran-3-carboxylate (1b):

A 50 mL oven-dried round-bottomed flask equipped with a septum, a magnetic stir bar and a nitrogen gas inlet was charged with dichloromethane (20 mL) and magnetically stirred in an ice-cold water bath for 5-10 min. To this diethyl zinc (0.135 mL, 1.312 mmol) was added followed by dropwise addition of diiodomethane (0.106 mL, 1.312 mmol). The reaction mixture was stirred for 10-12 min followed by the rapid addition of the α-carboxyester imide **54** (0.096 g, 0.328 mmol) in dichloromethane (3 mL). The reaction mixture was allowed to stir under ice-cold conditions for 0.5 h until benzaldehyde (0.067 mL, 0.656 mmol) was added. The reaction mixture was allowed to stir for 12 h and quenched using saturated ammonium chloride (10 mL). The crude reaction mixture was extracted with dichloromethane (2 x 15 mL) and the organic layers were washed with brine (2 x 15 mL). The combined organic layers were dried using anhydrous magnesium sulfate (*ca.* 2 g) and concentrated in vacuo to obtain a yellow viscous oil. After column chromatography **1a (**0.025 g, 33%) (R_f = 0.40, hexane:ethyl acetate, 2:1) was isolated as a pale yellowish oil and **1b** (0.014 g, 17% yield) (R_f = 0.26, hexane:ethyl acetate, 2:1) was isolated as a colorless solid (mp = 74-76^{o}C). The formation of the diastereomeric lactones 1a and 1b within the crude reaction mixture were confirmed by the presence of the following NMR resonances: ^{1}H NMR (400 MHz, $CDCl_3$) (**1a**): δ 7.54 – 7.28 (m, 5H), 5.66 (d, *J* = 7.1 Hz, 1H), 4.24 (ddt, *J* = 10.5, 7.2, 3.4, 3.4 Hz, 1H), 3.38 – 3.26 (m, 1H), 3.01 (dd, *J* = 17.9, 9.0 Hz, 1H), 2.91 (dd, *J* = 17.5, 9.3 Hz, 1H), 1.29 (t, *J* = 7.1, 7.1 Hz, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**1b**): δ 7.46 – 7.22 (m, 5H), 5.76 (d, *J* = 7.9 Hz, 1H), 3.87 – 3.59 (m, 3H), 3.10 (dd, *J* = 18.0, 5.0 Hz,

1H), 2.81 (dd, *J* = 18.0, 8.0 Hz, 1H), 0.87 (t, *J* = 7.2, 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (**1a**) δ 175.8, 171.2, 138.2, 129.1, 128.8, 125.6, 82.5, 62.2, 49.0, 32.5, 14.3. ^{13}C NMR (101 MHz, $CDCl_3$) (**1b**) δ 174.8, 169.8, 135.5, 129.1, 128.7, 125.9, 81.4, 61.5, 46.8, 31.8, 13.8.

(2*S*,3*R*)-ethyl 2-(4-methoxyphenyl)-5-oxotetrahydrofuran-3-carboxylate (2a) and (2*R*,3*R*)-ethyl 2-(4-methoxyphenyl)-5-oxotetrahydrofuran-3-carboxylate (2b):

A 50 mL oven-dried round-bottomed flask equipped with a septum, a magnetic stir bar and a nitrogen gas inlet was charged with dichloromethane (20 mL) and magnetically stirred in an ice-cold water bath for 5-10 min. To this diethyl zinc (0.088 mL, 0.856 mmol) was added followed by dropwise addition of diiodomethane (0.069 mL, 0.856 mmol). The reaction mixture was stirred for 10-12 min followed by the rapid addition of the α-carboxyester imide **54** (0.062 g, 0.214 mmol) in dichloromethane (3 mL). The reaction mixture was allowed to stir under ice-cold conditions for 0.5 h until *p*-anisaldehyde (0.051 mL, 0.428 mmol) was added. The reaction mixture was allowed to stir for 12 h and quenched using saturated ammonium chloride (10 mL). The crude reaction mixture was extracted with dichloromethane (2 x 15 mL) and the organic layers were washed with brine (2 x 15 mL). The combined organic layers were dried using anhydrous magnesium sulfate (*ca.* 2 g) and concentrated in vacuo to obtain a yellow viscous oil. After column chromatography **2a (**0.025 g, 45%) (R_f = 0.36, hexane:ethyl acetate, 2:1) was isolated as a pale yellowish oil and **2b** (0.011 g, 19% yield) (R_f= 0.26, hexane:ethyl acetate, 2:1) was isolated as a pale yellowish oil. The formation of the diastereomeric lactones 2a and 2b within the crude reaction mixture were confirmed by the presence of the following NMR resonances: ^{1}H NMR (500 MHz, $CDCl_3$) (**2a**): δ 7.37 – 7.20 (m, 2H), 7.00 – 6.83 (m, 2H), 5.58 (d, *J* = 7.6 Hz, 1H), 4.21 (tq, *J* = 7.1, 7.1, 3.6, 3.6, 3.6 Hz, 2H), 3.82 (s, 3H), 3.31 (td, *J* = 9.3, 9.3, 7.6 Hz, 1H), 3.00 (dd, *J* = 18.0, 9.0 Hz, 1H), 2.91 (dd, *J* = 18.0, 9.0 Hz, 1H), 1.26 (t, *J* = 7.1,

7.1 Hz, 3H). ^{1}H NMR (500 MHz, $CDCl_3$) (**2b**) δ 7.23 – 7.15 (m, 1H), 6.93 – 6.83 (m, 1H), 5.72 (d, *J* = 8.0 Hz, 1H), 3.94 – 3.58 (m, 5H), 3.10 (dd, *J* = 17.8, 5.7 Hz, 1H), 2.78 (dd, *J* = 17.8, 8.9 Hz, 1H), 0.92 (t, *J* = 7.2, 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) (**2a**) δ 174.2, 170.8, 160.1, 129.8, 127.1, 114.3, 82.4, 61.9, 55.4, 48.8, 32.6, 14.2.

(2*S*,3*R*)-ethyl 2-(*tert*-butyl)-5-oxotetrahydrofuran-3-carboxylate (3a) and (2*R*,3*R*)-ethyl 2-(*tert*-butyl)-5-oxotetrahydrofuran-3-carboxylate (3b):

A 50 mL oven-dried round-bottomed flask equipped with a septum, a magnetic stir bar and a nitrogen gas inlet was charged with dichloromethane (20 mL) and magnetically stirred in an ice-cold water bath for 5-10 min. To this diethyl zinc (0.114 mL, 1.104 mmol) was added followed by dropwise addition of diiodomethane (0.089 mL, 1.104 mmol). The reaction mixture was stirred for 10-12 min followed by the rapid addition of the α-carboxyester imide **54** (0.080 g, 0.276 mmol) in dichloromethane (3 mL). The reaction mixture was allowed to stir under ice-cold conditions for 0.5 h until trimethyl acetaldehyde (*pivaldehyde*) (0.061 mL, 0.552 mmol) was added. The reaction mixture was allowed to stir for 12 h and quenched using saturated ammonium chloride (10 mL). The crude reaction mixture was extracted with dichloromethane (2 x 15 mL) and the organic layers were washed with brine (2 x 15 mL). The combined organic layers were dried using anhydrous magnesium sulfate (*ca.* 2 g) and concentrated in vacuo to obtain a yellow viscous oil. After column chromatography **3a (**0.023 g, 39%) (R_f = 0.41, hexane:ethyl acetate, 2:1) was isolated as a pale yellowish oil and **3b** (0.011 g, 18% yield) (R_f = 0.36, hexane:ethyl acetate, 2:1) was isolated as a pale yellowish oil. The formation of the diastereomeric lactones 3a and 3b within the crude reaction mixture were confirmed by the presence of the following NMR resonances: ^{1}H NMR (500 MHz, $CDCl_3$) (**3a**): δ 4.42 (d, *J* = 6.4 Hz, 1H), 4.29 – 4.12 (m, 2H), 3.13 (ddd, *J* = 10.3, 7.5, 6.4 Hz, 1H), 2.89 (dd, *J* = 17.9, 8.0 Hz,

1H), 2.78 (dd, *J* = 18.0, 9.0 Hz, 1H), 1.29 (t, *J* = 7.2, 7.2 Hz, 3H), 0.97 (s, 9H). ^{1}H NMR (500 MHz, $CDCl_3$) (**3b**): δ 4.23 (d, *J* = 5.9 Hz, 1H), 4.22 – 4.08 (m, 2H), 3.31 (ddd, *J* = 7.8, 6.0, 2.8 Hz, 1H), 2.80 (dd, *J* = 17.0, 3.0 Hz, 1H), 2.66 (dd, *J* = 17.0, 8.0 Hz, 1H), 1.28 (t, *J* = 7.2, 7.2 Hz, 3H), 1.03 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) (**3a**): δ 174.7, 172.4, 89.4, 61.8, 41.1, 34.7, 33.1, 24.9, 14.1. ^{13}C NMR (126 MHz, $CDCl_3$) (**3b**): δ 175.8, 171.4, 89.0, 61.5, 43.5, 34.7, 34.1, 25.7, 13.8.

(2*R*,3*R*)-ethyl 5-oxo-2-phenethyltetrahydrofuran-3-carboxylate (4b):

A 50 mL oven-dried round-bottomed flask equipped with a septum, a magnetic stir bar and a nitrogen gas inlet was charged with dichloromethane (20 mL) and magnetically stirred in an ice-cold water bath for 5-10 min. To this diethyl zinc (0.105 mL, 1.052 mmol) was added followed by dropwise addition of diiodomethane (0.088 mL, 1.052 mmol). The reaction mixture was stirred for 10-12 min followed by the rapid addition of the α-carboxyester imide **54** (0.081 g, 0.263 mmol) in dichloromethane (3 mL). The reaction mixture was allowed to stir under ice-cold conditions for 0.5 h until 3-phenyl-1-propanal (*hydrocinnamaldehyde*) (0.069 mL, 0.526 mmol) was added. The reaction mixture was allowed to stir for 12 h and quenched using saturated ammonium chloride (10 mL). The crude reaction mixture was extracted with dichloromethane (2 x 15 mL) and the organic layers were washed with brine (2 x 15 mL). The combined organic layers were dried using anhydrous magnesium sulfate (*ca.* 2 g) and concentrated in vacuo to obtain a yellowish-orange viscous oil. After column chromatography **4b (**0.025 g, 37%) (R_f = 0.26-0.28, hexane:ethyl acetate, 2:1) was isolated as a pale yellowish oil and was isolated as a pale yellowish oil. The formation of the diastereomeric lactone 4b within the crude reaction mixture was confirmed by the presence of the following NMR resonances: ^{1}H NMR (500 MHz, $CDCl_3$) (**4b**): δ 7.41 – 7.26 (m, 2H), 7.25 – 7.13 (m, 3H), 4.60 (ddd, *J* = 10.6, 7.4, 3.8 Hz, 1H),

4.21 (q, *J* = 7.1, 7.1, 7.1 Hz, 2H), 3.46 – 3.34 (m, 1H), 2.98 – 2.83 (m, 2H), 2.80 – 2.61 (m, 2H), 2.00 – 1.80 (m, 2H), 1.27 (t, *J* = 7.2, 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) (**4b**): δ 175.2, 170.2, 140.3, 128.6, 128.5, 126.3, 79.1, 61.6, 44.2, 33.0, 31.8, 14.2.

(R)-ethyl 2,2-dimethyl-5-oxotetrahydrofuran-3-carboxylate (5):

A 50 mL oven-dried round-bottomed flask equipped with a septum, a magnetic stir bar and a nitrogen gas inlet was charged with dichloromethane (20 mL) and magnetically stirred in an ice-cold water bath for 5-10 min. To this diethyl zinc (0.053 mL, 0.516 mmol) was added followed by dropwise addition of diiodomethane (0.042 mL, 0.516 mmol). The reaction mixture was stirred for 10-12 min followed by the rapid addition of the α-carboxyester imide **54** (0.050 g, 0.172 mmol) in dichloromethane (3 mL). The reaction mixture was allowed to stir under ice-cold conditions for 0.5 h until 2-Propanone (*Acetone*) (0.020 mL, 0.258 mmol) was added. The reaction mixture was allowed to stir for 12 h and quenched using saturated ammonium chloride (10 mL). The crude reaction mixture was extracted with dichloromethane (2 x 15 mL) and the organic layers were washed with brine (2 x 15 mL). The combined organic layers were dried using anhydrous magnesium sulfate (*ca.* 2 g) and concentrated in vacuo to obtain yellowish viscous oil. After column chromatography **5 (**0.023 g, 72%) (R_f = 0.45-0.48, hexane:ethyl acetate, 2:1) was isolated as a colorless oil. The formation of the diastereomeric lactone **5** within the crude reaction mixture was confirmed by the presence of the following NMR resonances: ^{1}H NMR (500 MHz, $CDCl_3$) (**5**): δ 4.31 – 4.14 (m, 2H), 3.23 – 3.14 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.09 (dd, *J* = 17.5, 9.0 Hz, 1H), 2.70 (dd, *J* = 17.7, 8.6 Hz, 1H), 1.61 (s, 3H), 1.36 – 1.27 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) (**5**): δ 174, 169.8, 84.4, 61.6, 50.5, 31.8, 28.6, 23.3, 14.2.

(2R,3R)-ethyl 2-(4-chlorophenyl)-2-methyl-5-oxotetrahydrofuran-3-carboxylate (6a) and (2S,3R)-ethyl 2-(4-chlorophenyl)-2-methyl-5-oxotetrahydrofuran-3-carboxylate (6b):

A 50 mL oven-dried round-bottomed flask equipped with a septum, a magnetic stir bar and a nitrogen gas inlet was charged with dichloromethane (20 mL) and magnetically stirred in an ice-cold water bath for 5-10 min. To this diethyl zinc (0.070 mL, 0.673 mmol) was added followed by dropwise addition of diiodomethane (0.055 mL, 0.673 mmol). The reaction mixture was stirred for 10-12 min followed by the rapid addition of the α-carboxyester imide **54** (0.065 g, 0.224 mmol) in dichloromethane (3 mL). The reaction mixture was allowed to stir under ice-cold conditions for 0.5 h until *p*-chloroacetophenone (0.058 mL, 0.448 mmol) was added. The reaction mixture was allowed to stir for 12 h and quenched using saturated ammonium chloride (10 mL). The crude reaction mixture was extracted with dichloromethane (2 x 15 mL) and the organic layers were washed with brine (2 x 15 mL). The combined organic layers were dried using anhydrous magnesium sulfate (*ca.* 2 g) and concentrated in vacuo to obtain yellowish viscous oil. After column chromatography **6a (**0.025 g, 46%) (R_f = 0.45-0.48, hexane:ethyl acetate, 2:1) and **6b (**0.013 g, 21%) (R_f = 0.25-0.28, hexane:ethyl acetate, 2:1) was isolated as a pale yellow to colorless oil. The formation of the diastereomeric lactone **6a** and **6b** within the crude reaction mixture was confirmed by the presence of the following NMR resonances: ^{1}H NMR (500 MHz, $CDCl_3$) (**6a**): δ 7.47 – 7.32 (m, 4H), 4.37 – 4.20 (m, 2H), 3.46 (dd, *J* = 8.8, 6.1 Hz, 1H), 3.03 (dd, *J* = 17.8, 6.1 Hz, 1H), 2.65 (dd, *J* = 17.8, 8.8 Hz, 1H), 1.66 (s, 3H), 1.34 (t, *J* = 7.1, 7.1 Hz, 3H). ^{1}H NMR (500 MHz, $CDCl_3$) (**6b**): δ 7.38 – 7.22 (m, 4H), 3.91 – 3.69 (m, 2H), 3.43 (dd, *J* = 8.7, 6.1 Hz, 1H), 2.99 (dd, *J* = 18.0, 6.5 Hz, 1H), 2.85 (dd, *J* = 17.5, 8.0 Hz, 1H), 1.89 (s, 3H), 0.99 (t, *J* = 7.2, 7.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) (**6a**): δ 173.8, 170.1,

143.3, 134.2, 128.9, 125.9, 86.4, 61.9, 51.5, 31.9, 25.1, 14.2. ^{13}C NMR (126 MHz, $CDCl_3$) (**6b**): δ 174.2, 169.5, 138.4, 134.4, 128.5, 126.5, 86.7, 61.5, 52.4, 32.1, 28.9, 13.7.

(2S,3S)-ethyl 5-oxo-2-(p-tolyl)tetrahydrofuran-3-carboxylate (7a) and (2S,3R)-ethyl 5-oxo-2-(p-tolyl)tetrahydrofuran-3-carboxylate (7b):

A 50 mL oven-dried round-bottomed flask equipped with a septum, a magnetic stir bar and a nitrogen gas inlet was charged with dichloromethane (20 mL) and magnetically stirred in an ice-cold water bath for 5-10 min. To this diethyl zinc (0.15 mL, 1.392 mmol) was added followed by dropwise addition of diiodomethane (0.12 mL, 1.392 mmol). The reaction mixture was stirred for 10-12 min followed by the rapid addition of the α-carboxyester imide **99** (0.070 g, 0.348 mmol) in dichloromethane (3 mL). The reaction mixture was allowed to stir at room temperature for 1 h and brought to ice-cold conditions. At this time, *p*-tolualdehyde (0.082 mL, 0.696 mmol) was added and the reaction mixture was allowed to stir for 12 h and quenched using saturated ammonium chloride (10 mL). The crude reaction mixture was extracted with dichloromethane (2 x 15 mL) and the organic layers were washed with brine (2 x 15 mL). The combined organic layers were dried using anhydrous magnesium sulfate (*ca.* 2 g) and concentrated in vacuo to obtain yellowish viscous oil. After column chromatography **7a (**0.035 g, 41%) (R_f = 0.45-0.48, hexane:ethyl acetate, 2:1) was isolated and **7b (**0.013 g, 15%) (R_f = 0.25-0.28, hexane:ethyl acetate, 2:1) were isolated as pale yellow to colorless oils. The formation of the diastereomeric lactones **7a** and **7b** within the crude reaction mixture was confirmed by the presence of the following NMR resonances: ^{1}H NMR (400 MHz, $CDCl_3$) (**7a**): δ 7.26 – 7.19 (m, 4H), 5.62 (d, *J* = 7.3 Hz, 1H), 4.22 (tdd, *J* = 10.8, 10.8, 6.9, 3.7 Hz, 2H), 3.39 – 3.23 (m, 1H), 3.09 (dd, *J* = 18.0 Hz, 9.0 Hz, 1H), 2.83 (dd, *J* = 18.0 Hz, 9.0 Hz, 1H), 2.37 (s, 3H), 1.27 (t, *J* = 7.1, 7.1 Hz, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) (**7b**): δ 7.24 – 7.08 (m, 4H), 5.73 (d, *J* = 7.9 Hz, 1H), 3.91 – 3.61

(m, 4H), 3.10 (dd, *J* = 17.7, 5.6 Hz, 1H), 2.78 (dd, *J* = 17.7, 8.7 Hz, 1H), 2.34 (s, 3H), 0.91 (t, *J* = 7.1, 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (**7a**): δ 174.5, 171.0, 139.1, 135.2, 129.7, 125.7, 82.6, 62.1, 49.0, 32.6, 21.4, 14.3. ^{13}C NMR (101 MHz, $CDCl_3$) (**7b**): δ 175.3, 169.8, 139.0, 132.5, 129.3, 125.9, 81.4, 61.5, 46.9, 31.7, 21.4, 13.8.

(2S,3S)-ethyl 2-(furan-2-yl)-5-oxotetrahydrofuran-3-carboxylate (8a):

A 50 mL oven-dried round-bottomed flask equipped with a septum, a magnetic stir bar and a nitrogen gas inlet was charged with dichloromethane (20 mL) and magnetically stirred in an ice-cold water bath for 5-10 min. To this diethyl zinc (0.17 mL, 1.632 mmol) was added followed by dropwise addition of diiodomethane (0.14 mL, 1.632 mmol). The reaction mixture was stirred for 10-12 min followed by the rapid addition of the α-carboxyester imide **99** (0.082 g, 0.408 mmol) in dichloromethane (3 mL). The reaction mixture was allowed to stir at room temperature for 1 h and brought to ice-cold conditions. At this time, 2-Furaldehyde (*Furfural*) (0.070 mL, 0.816 mmol) was added and the reaction mixture was allowed to stir for 12 h and quenched using saturated ammonium chloride (10 mL). The crude reaction mixture was extracted with dichloromethane (2 x 15 mL) and the organic layers were washed with brine (2 x 15 mL). The combined organic layers were dried using anhydrous magnesium sulfate (*ca.* 2 g) and concentrated in vacuo to obtain yellowish viscous oil. After column chromatography **7a (**0.040 g, 45%) (R_f = 0.45-0.48, hexane:ethyl acetate, 2:1) was isolated as a pale yellow to colorless oil. The formation of the diastereomeric lactone **8a** within the crude reaction mixture was confirmed by the presence of the following NMR resonances: ^{1}H NMR (500 MHz, $CDCl_3$) (**8a**): δ 7.51 – 7.41 (m, 1H), 6.54 – 6.45 (m, 1H), 6.39 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.66 (d, *J* = 6.3 Hz, 1H), 4.22 (q, *J* = 7.1, 7.1, 7.1 Hz, 2H), 3.66 (ddd, *J* = 9.4, 7.7, 6.4 Hz, 1H), 3.12 – 2.90 (m, 2H), 1.27 (t, *J* =

7.1, 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) (**8a**): δ 173.8, 170.5, 149.3, 143.9, 110.7, 110.3, 75.5, 62.0, 53.4, 44.5 32.0, 14.1.

References

1) Mussato, M. C.; Savoia, D.; Trombini, C.; Umani Ronchi, A. *J. Org. Chem.* **1980**, *45*, 4002.

2) Bieräugel, H.; Akkerman, J. M.; Armande, J. C. L.; Pandit, U. K. *Tetrahedron Lett.* **1974,** *15*, 2817.

3) Saigo, K.; Kurihara, H.; Miura, H.; Hongu, A.; Kubota, N.; Nohira, H.; Hasegawa, M. *Synth. Commun.* **1984,** *14* (Copyright © 2012 American Chemical Society (ACS). All Rights Reserved.), 787.

4) Dowd, P.; Choi, S. C. *J. Am. Chem. Soc.* **1987,** *109*, 3493.

5) Grimm, E. L.; Reissig, H. U. *J. Org. Chem.* **1985,** *50*, 242.

6) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*. 804.

7) Brogan, J. B.; Zercher, C. K. *J. Org. Chem.* **1997**, *62*, 6444.

8) (a) Furukawa J, Kawabata N, Nishimura J. *Tetrahedron Lett.* **1966**, *7*: 3353. (b) Furukawa J, Kawabata N, Nishimura J. *Tetrahedron Lett.* **1968**, *24*: 53. (c) Lehnert E.K.; Sawyer, S. J.; Macdonald. T. L. *Tetrahedron Lett.* **1989**, *30*: 5215. (d) Charette, A. B, Marcoux, J. F. *J. Am. Chem. Soc.* **1996**, *118:* 4539.

9) Lai, S.; Zercher, C. K.; Jasinski, J. P.; Reid, S. N.; Staples, R. J. *Org. Lett.* **2001,** *3*, 4169.

10) Jacobine, A. M.; Puchlopek, A. L. A.; Zercher, C. K.; Briggs, J. B.; Jasinski, J. P.; Butcher, R. J. *Tetrahedron* **2012,** *68*, *38*, 7799.

11) Ronsheim, M. D.; Zercher, C. K. *J. Org. Chem.* **2002**, *68*, 4536.

12) Hilgenkamp, R.; Zercher, C. K. *Org. Lett.* **2001,** *3*, 3037.

13) Verbicky, C. A.; Zercher, C. K. *J. Org. Chem.* **2000,** *65*, 5615.

14) Lin, W.; Theberge, C.R.; Henderson, T. J.; Zercher, C. K.; Jasinski, J.; Butcher, R. J. *J. Org. Chem.* **2009**, *74*, 645.

15) Sadlowski, C. B.S. Thesis. *University of New Hampshire* **2007**.

16) Henderson, T. J., M.S. Thesis. *University of New Hampshire* **2009**.

17) Pu, Q.; Wilson, E.; Zercher, C. K. *Tetrahedron*. **2008**, *64*, 8045.

18) Brik. A.; Wong, C. H. *Org. Bimol. Chem*. **2003**, *1*, 5.

19) Heim, R.; Wiedemann, S.; Williams, C. M.; Bernhardt, P. V. *Org. Lett.* **2005**, *7*: 1327.

20) Schwartz, B. D.; Tilly, D. P.; Heim, R.; Wiedemann, S.; Williams, C. M.; Bernhardt, P. V. *Eur J. Org. Chem.* **2006**, *2006*, 3181.

21) Aiken, K. S. Ph.D. Dissertation. *University of New Hampshire*. **2005**.

22) Aiken, K. S.; Eger, W. A.; Williams, C. M.; Spencer, C. M.; Zercher, C. K. *J. Org. Chem.* **2012**, *77*, 5942-5955.

23) Chen, C. A.; Sieburth, S. M.; Glekas, A.; Hewitt, G. W.; Trainor, G. L.; Erickson-Viitanen, S.; Garber, S. S.; Cordova, B; Jeffrey, S.; Klabe, R. M. *Chem. Bio.* **2001**, *8*, 1161-1166.

24) Wipf, P.; Xiao, J. *Org. Lett.* **2005**, *7*, 103-106.

25) Martin, S. F.; Dorsey, G. O.; Gane, T.; Hillier, M. C.; Kessler, H.; Baur, M.; Mathae, B.; Erickson, J. W.; Bhat, T. N.; Munshi, S.; Gulnik, S. V.; Topol, I. A. *J. Med. Chem.* **1998**, *41*, 1581-1597.

26) Taschner, I. Ph.D. dissertation. *University of New Hampshire*. **2005**.

27) Meerwein, H.; Schmidt, R. *Justus Liebigs Annalen der Chemie.* **1925**, 221-238.

28) Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621.

29) Lorenz, J. C.; Long, J.; Yang, Z. Q.; Xue, S.; Xie, Y. N.; Shi, Y. *J. Org. Chem.* **2004**, *69*, 327.

30) Eger, W. A.; Zercher, C. K.; Williams, C. M. *J. Org. Chem.* **2010**, *75*, 7322.

31) Xue, S.; Li, L.Z.; Liu, Y. K.; Guo, Q. X. *J. Org. Chem.* **2006,** *71,* 215.

32) Mower, M. B.S. Thesis. *University of New Hampshire.* **2012**.

33) Chhetri, R. K. B. Unpublished results. *University of New Hampshire.* **2017**.

34) Moran, P. M.S. Thesis. *University of New Hampshire*. **2013**.

35) Bhogadhi, Y. M. D. Ph.D. dissertation. *University of New Hampshire.* **2015**.

36) Klein, R.A. Ph.D. dissertation, *Iowa State University*. **1965**.

37) Anslyn, E. V.; Dougherty, D. A. *Modern physical organic chemistry*. **2006**, ISBN: 1-891389-31-9.

38) Li, Z. L.; Xiao, B.; Guo, X.Q.; Song, X. *Tetrahedron Lett.* **2006**, *62*, 7762.

39) Cha, J. K.; Das, P. P.; Parida, B. B. *Arkivoc*. **2012**, *2*, 74.

40) Cheng, K.; Caroll, P. J.; Walsh, P. J. *Org. Lett.* **2011**, *13*, 2346.

41) (a) Nickon, A.; Lambert, J. L. *J. Am. Chem. Soc.* **1962**, *84*, 4604. **(b)** Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 7360. **(c)** Hirai, Y.; Terada, T.; Yamazaki, T. *J. Am. Chem. Soc.* **1988**, *110*, 958. **(d)** Martins, E. O.; Gleason, J. L. *Org. Lett.* **1999**, *1*, 1643.

42) (a) Gibson, D. H.; DePuy, C. H. *Chem. Rev.* **1974**, *74*, 605. (b). Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *1*, 155.

43) Hoyano, Y.; Patel, V.; Stothers, J. B. *Can. J. Chem.* **1980**, *58*, 2730.

44) Charette, A.B.; Voituriez, A.; Zimmer, L.E. *J. Org. Chem.* **2010**, *75*, 1244.

45) Lacasse, M. C.; Poulard, C.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 12440.

46) Lin, W.M.; McGinness, R.J.; Wilson, E. C.; Zercher, C. K. *Synthesis.* **2007**, *15*, 2404.

47) (a) Venkataramani, P. S.; Karoglan, J. E.; Reusch, W. *J. Am. Chem. Soc.* **1971**, *93*, 269. (b) Grimm, K.; Venkataramani, P. S.; Reusch, W. *ibid.* **1971**, *93*, 269.

48) (a) Hamon, D. P. G.; Sinclair, R. W. *Chem. Comm.* **1968**, 890. (b) Freeman, J. P.; Plonka, J. H. *J. Am. Chem. Soc.* **1966**, *88*, 3662.

49) (a) Wharton, P. S.; Bair, T. L. *J. Org. Chem.* **1966**, *31*, 2480. (b) Wharton, P. S.; Fritzberg, A. R. *J. Org. Chem.* **1972**, *37*, 1899.

50) Guthrie, P.J.; Guo, J. *J. Am. Chem. Soc.* **1996**, *118*, 11472.

51) (a) Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis,* 2nd ed.; Wiley: New York, **1991**. (b) Kocienski, P.J., *Protecting Groups*; Thieme: Stuttgart, **1994**.

52) Xie, C.; Runnegar, M.T.C.; Snider, B.B. *J. Am. Chem. Soc.* **2000**, *122*, 5018.

53) Laxminarayana, E.; Kumar, N.V.; Sridhar, G.; Mallaiah, B.; Giri, T. IJPI's *Journal of Drug Chem.* **2012**, *10*, 2.

54) Acheson, R. M. *Accounts Chem. Res.* **1971**, *4*, 177.

55) DePuy, C. H.; Breitbeil, F. W.; DeBruin, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 3347.

56) Clark, J. P. Ph.D. dissertation. *Univeristy of Colorado*. **1968**.

57) Risatti, C. B.S. Thesis. *University of New Hampshire.* **2000**.

58) Bhogadhi, Y. M. D.; Zercher, C. K. *Org. Synth.* **2014**, *91*, 248.

59) Csakai, A. B.S. Thesis. *University of New Hampshire.* **2006**.

60) Lin, W. I. Ph.D. dissertation. *University of New Hampshire.* **2006**.

61) Dekker, J.; Budzelaar, P. H. M.; Boersma, J.; Vanderkerk, G. J. M.; Spek, A. L. *Organometallics*, **1984**, *3*, 1403.

62) Dekker, J.; Budzelaar, P. H. M.; Boersma, J.; Vanderkerk, G. J. M. *J. Chem. Soc. Chem. Comm.* **1983**, 553.

63) Dewar, M. J. S.; Merz, K. M. *J. Am. Chem. Soc.* **1987**, *109*, 6553.

64) Tietze, L.F.; Schunke, C. *Eur. J. Org. Chem.* **1998**, 2089.

65) Fukunishi, K.; Inoue, Y.; Kishimoto, Y.; Mashio, F. *J. Org. Chem.* **1975**, *40*, 628.

66) Forzato, C.; Furlan, G.; Nitti, P.; Pitacco, G.; Valentin, E.; Zangrando, E.; Buzzini, P.; Goretti, M.; Turchetti, B. *Tetrahedron: Assymetry.* **2008**, *19*, 2026.

67) Fagnoni, M.; Bonassi, F.; Palmieri, A.; Protti, S.; Ravelli, D.; Ballini, R. *Adv. Synth. Catal.* **2014**, *356*, 753.

68) Shimada, S.; Hashimoto, Y.; Nagashima, T.; Hasegawa, M.; Saigo, K. *Tetrahedron*. **1993**, *49*, 1589.

69) Jacobine, A. M.; Lin, W.; Walls, B.; Zercher, C. K. *J. Org. Chem.* **2008**, *73*, 7409.

70) Patrick, T. M.; Erikson, F. B. *U.S. Pharmacoepia*. **1960**, *926*, 173.

71) Smith, M.B.; March, J. *Protective Groups in Organic Synthesis,* 8th ed.; Wiley: New York, **2007**.

72) Mondral, S.; Ghosh, S. *Tetrahedron*. **2008**, *64*, 2359.

73) Xavier, N.M.; Rauter, A.P.; Queneau, Y. *Top Curr. Chem*. **2010**, *61*, 22.

74) Charette, A.B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651

75) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

76) Montalbetti, C. A. G. N; Falque, V. *Tetrahedron*. **2005**, *61*, 10831.

77) Kleinback, F.; Fettes, G. J.; Fader, L. D.; Carreira, E. M. *Chem. Eur. J.* **2012**, *18*, 3598.

78) Mahy, W.; Plucinski, P. K.; Frost, C. G. *Org. Lett*. **2014**, *16*, 5020.

79) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757.

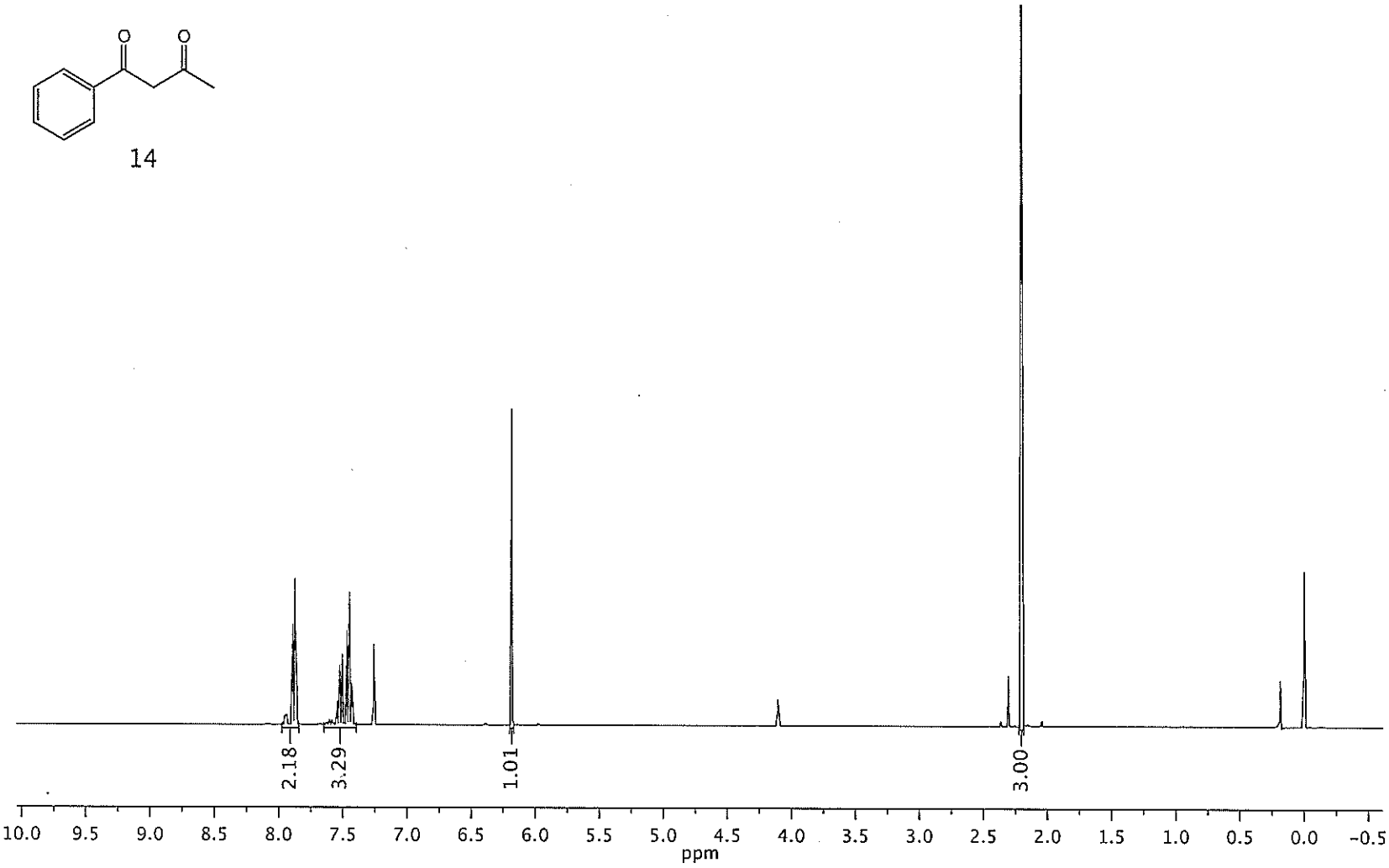
80) Verkade, J. G.; Tang, J. *Tetrahedron Lett*. **1993**, *34*, 2903.

81) Schwesinger, R.; Hasenfratz, C.; Schlemper, H.; Walz, L.; Peters, E. M.; Peters, K.; vonSchnering, H. G. *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 1361.

82) Pohmakotr, M.; Reutrakul, V.; Phongpradit, T.; Chansri, A. *Chem. Lett. The Chem. Soc of Jap.* **1982**, *5*, 687.

83) Comini, A.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *Tetrahedron: Assym.* **2004**, *15*, 618.

84) Danda, H.; Hansen, M. N.; Heathcock, C. H. *J. Org. Chem*. **1990**, *55*, 173.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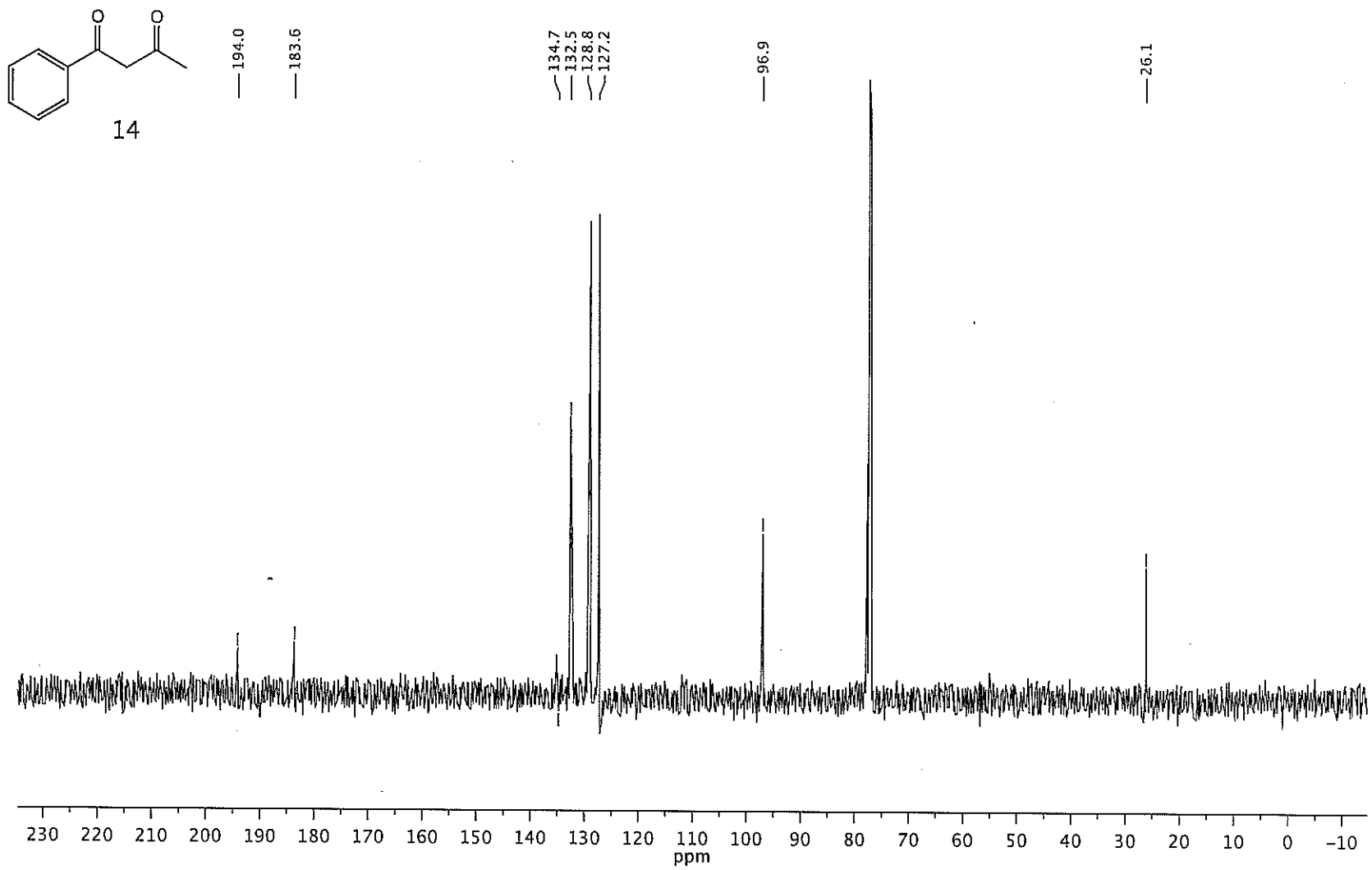
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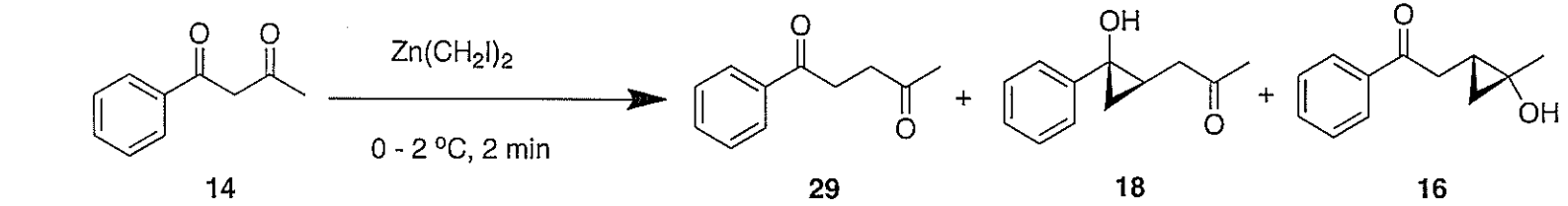
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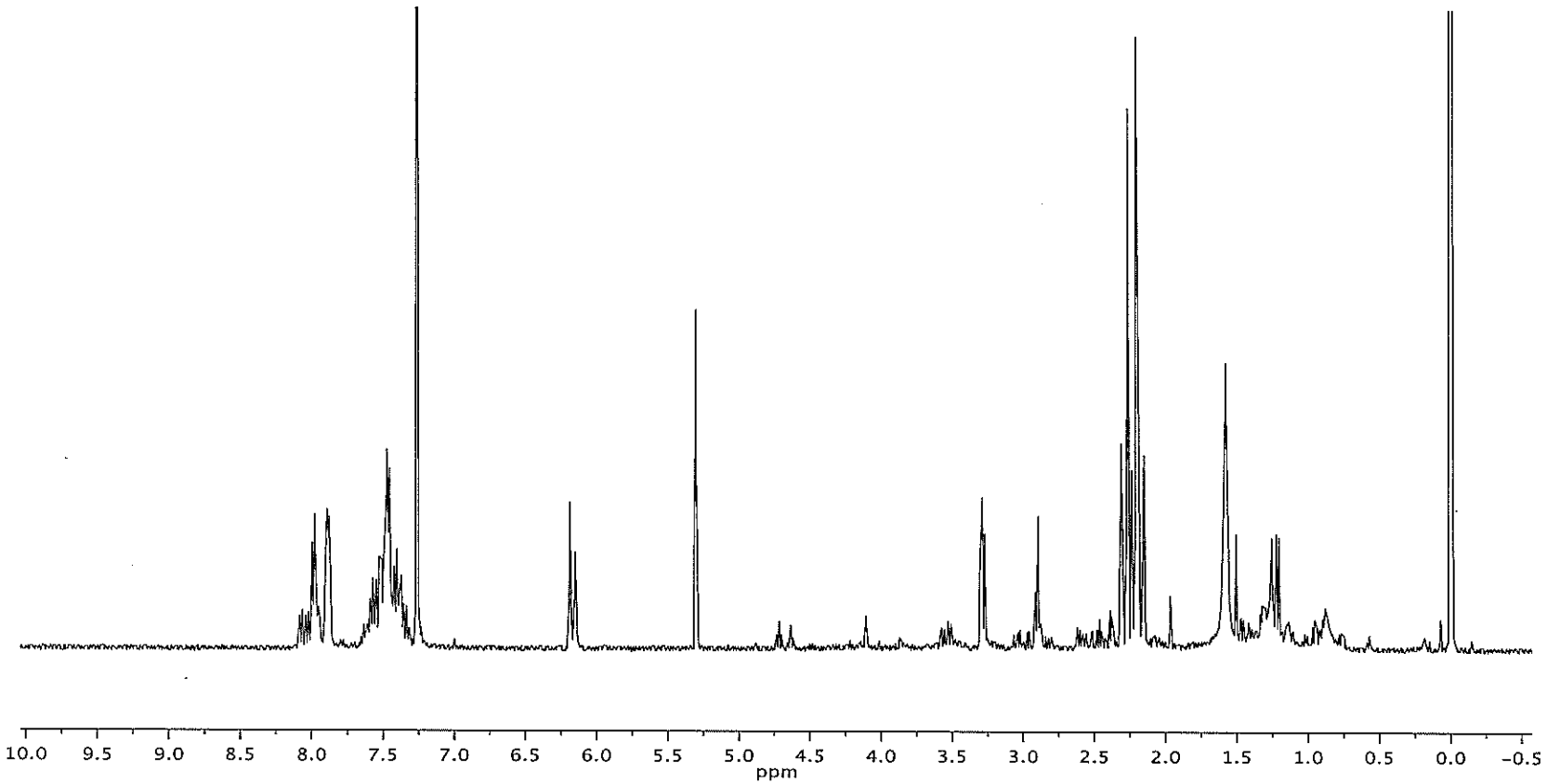
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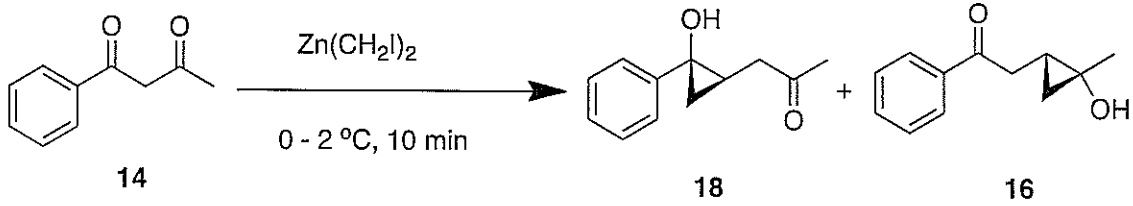
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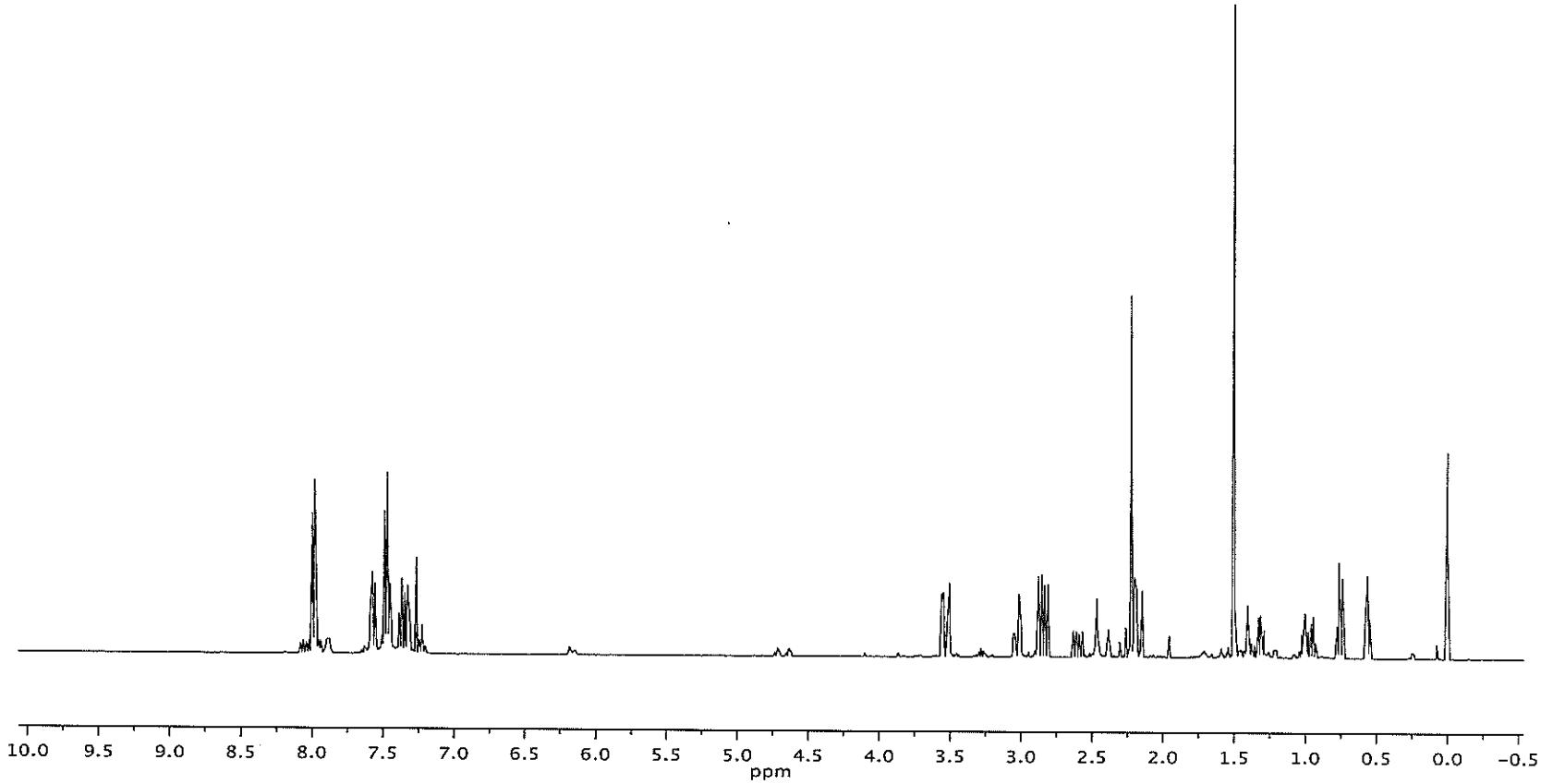
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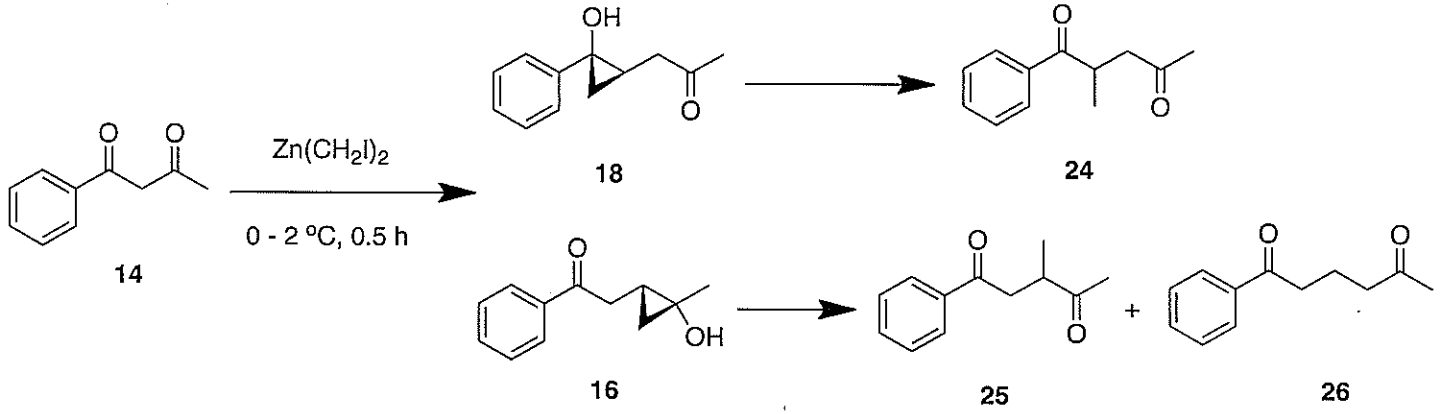
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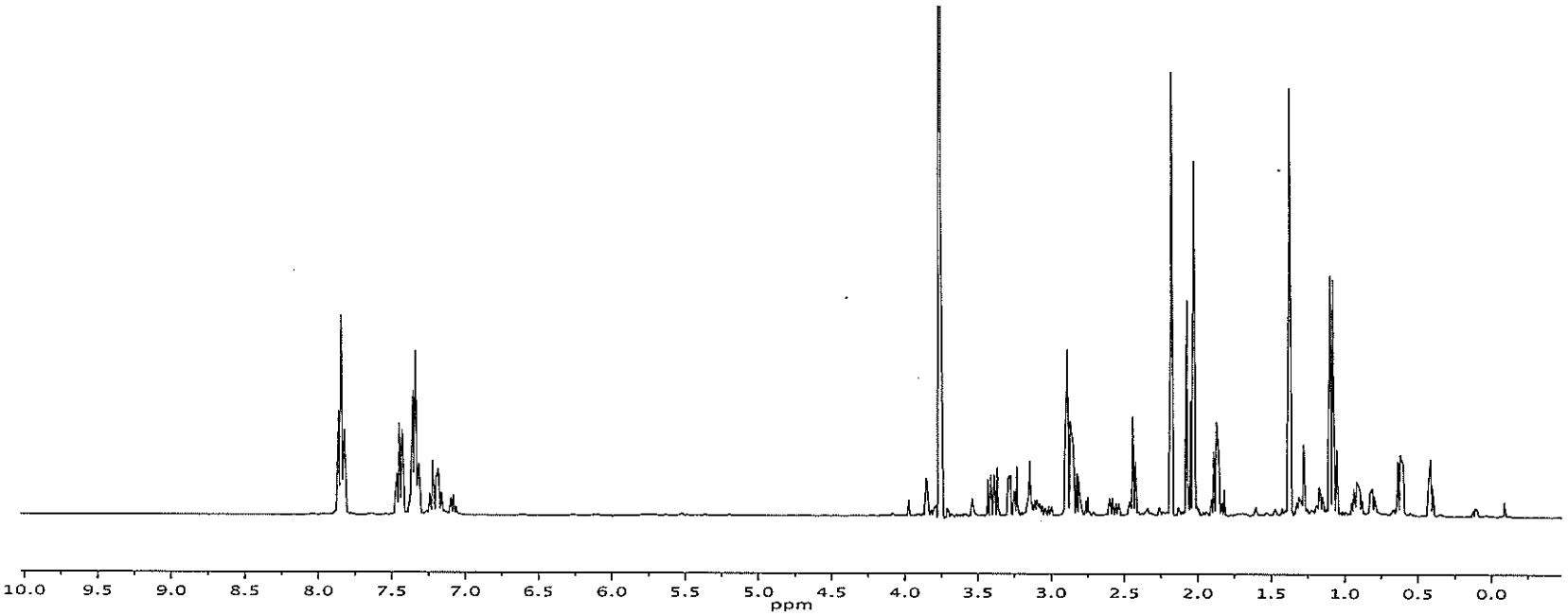
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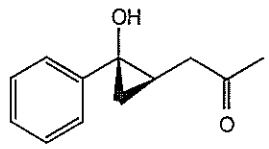
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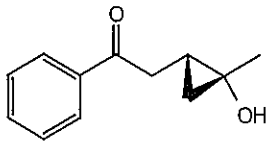
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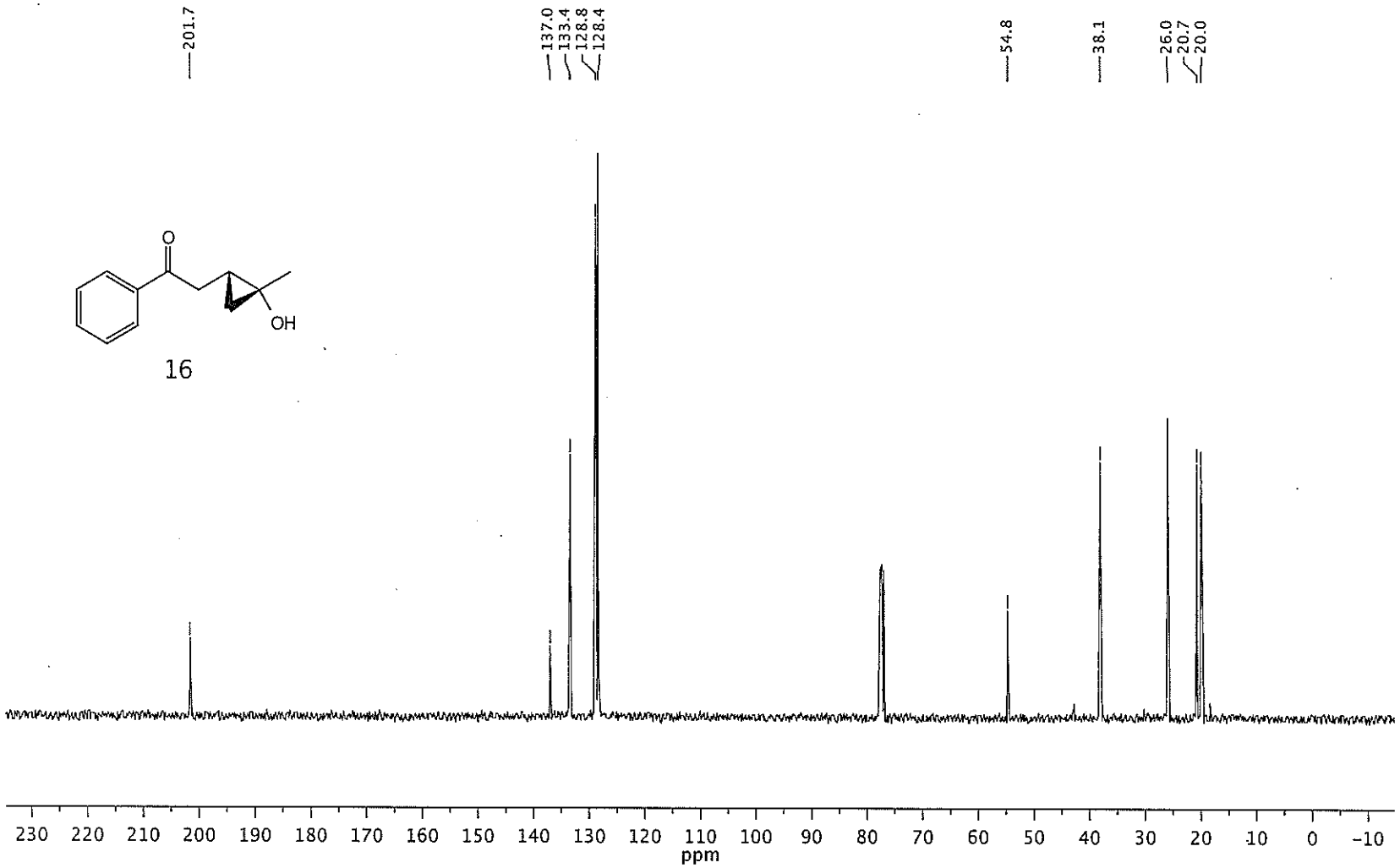
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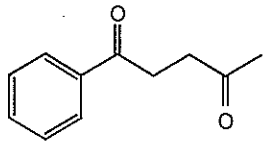
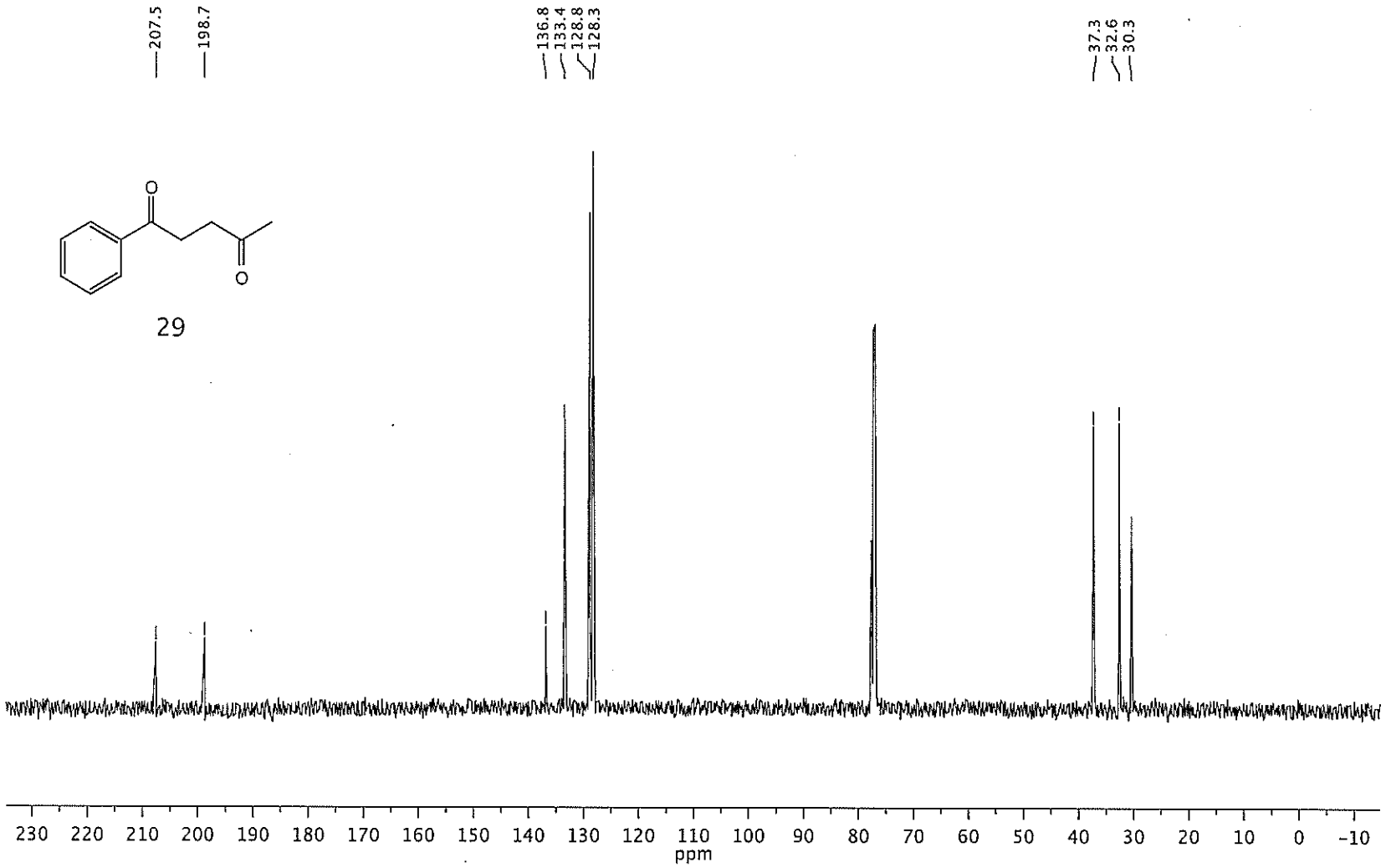
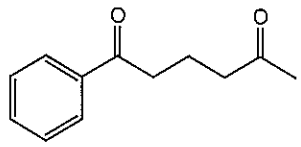
54.8
38.1
26.0
20.7
20.0
O
OH
16
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



29

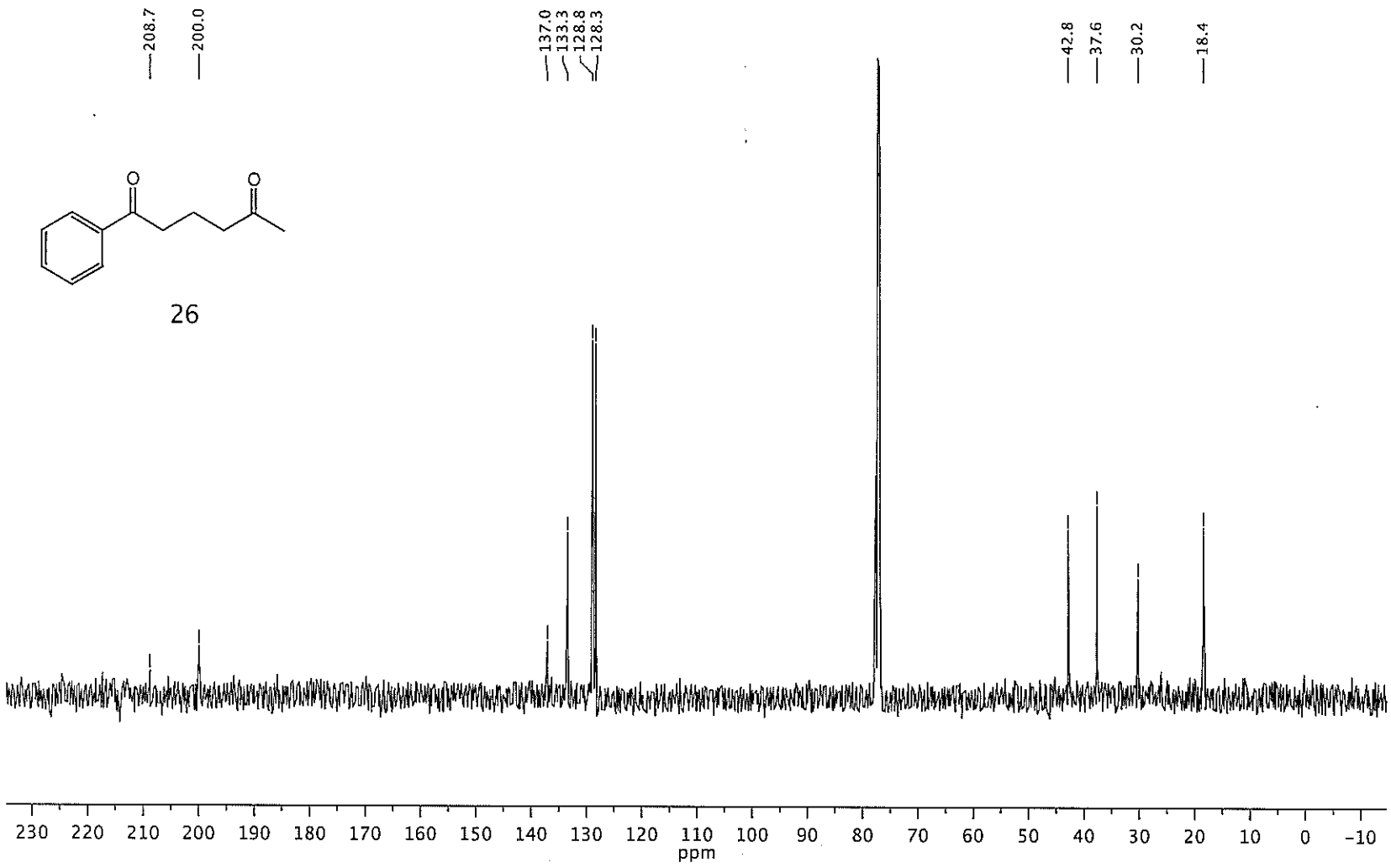
2.16
3.34
2.25
2.24
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

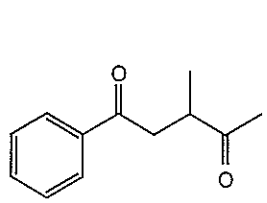

207.5
198.7
136.8
133.4
128.8
128.3
37.3
32.6
30.3
O
O
29
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



26

2.28
3.69
2.38
2.32
3.00
2.33
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

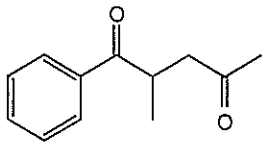

208.7
200.0
137.0
133.3
128.8
128.3
42.8
37.6
30.2
18.4
O
O
26
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



25

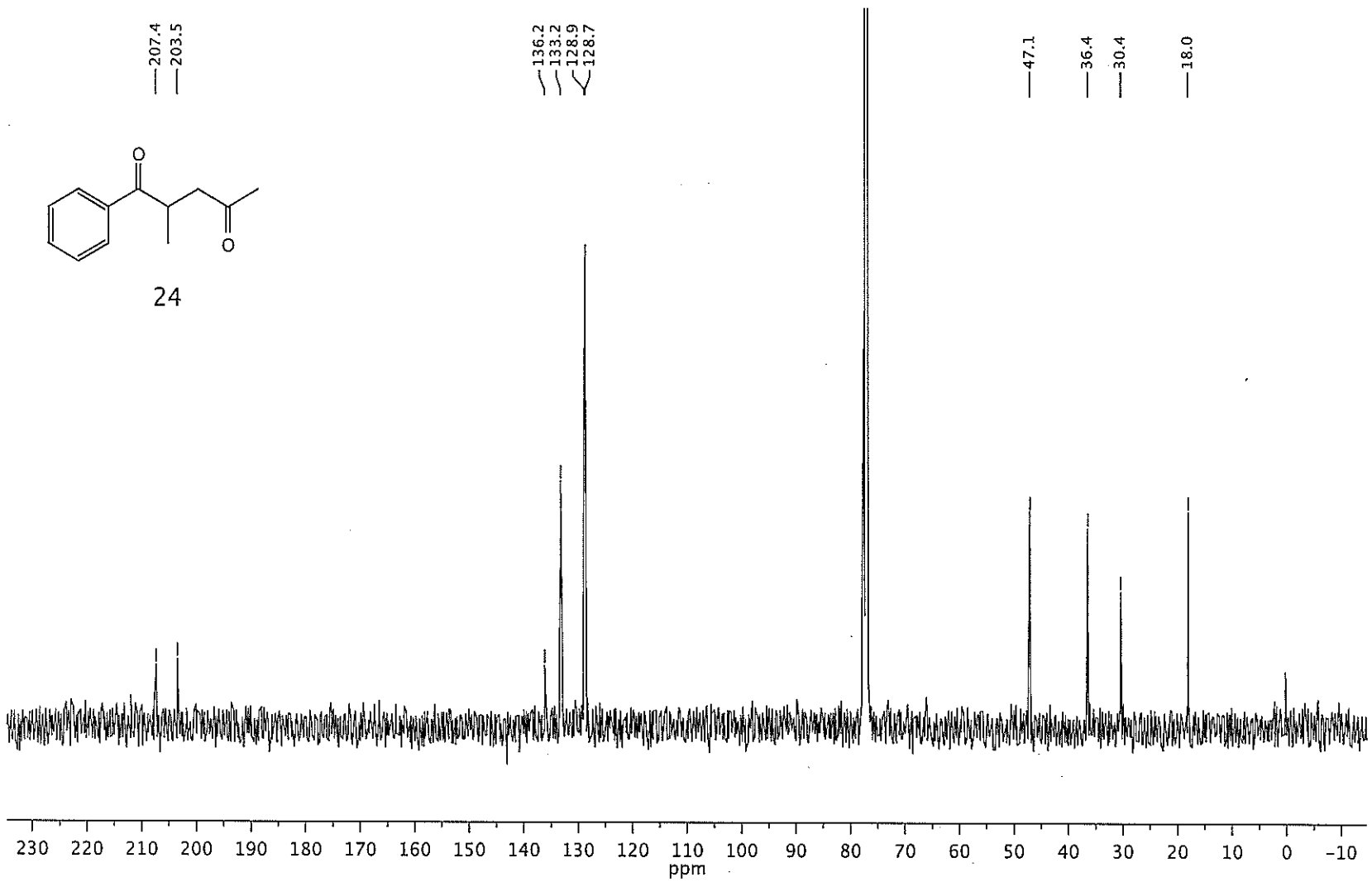
1.90
2.91
1.06
1.00
1.05
3.00
3.11
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

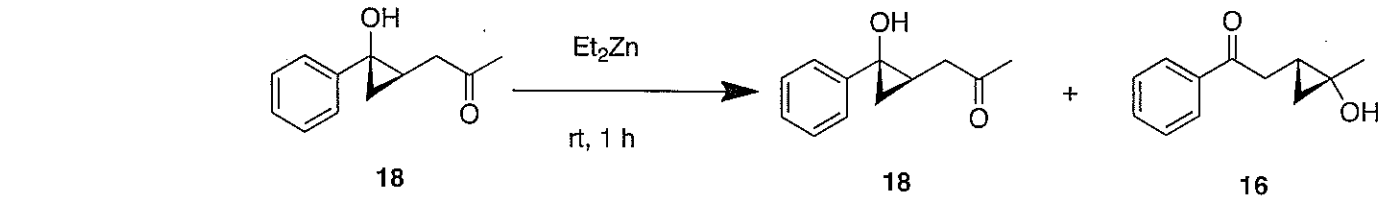
211.7
198.7
136.8
133.4
128.8
128.2
42.0
41.9
28.9
17.0
O
O
25
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



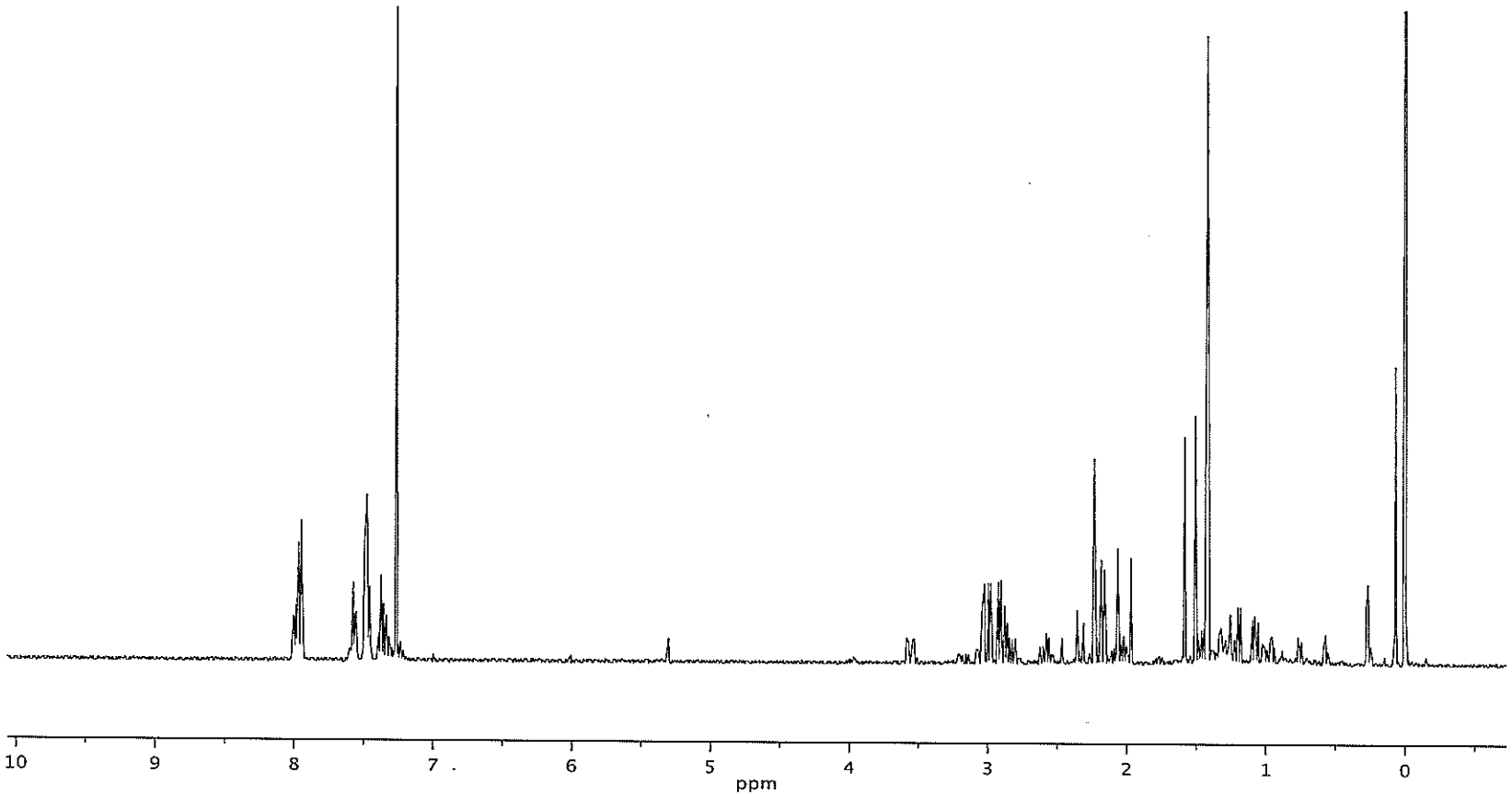
24

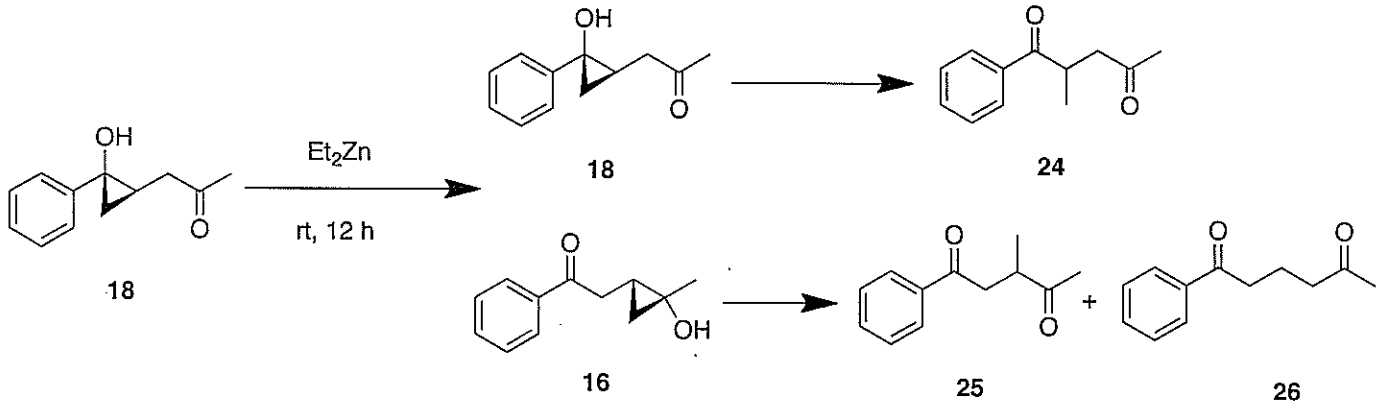
1.88
2.90
1.14
1.11
1.16
3.00
2.85
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

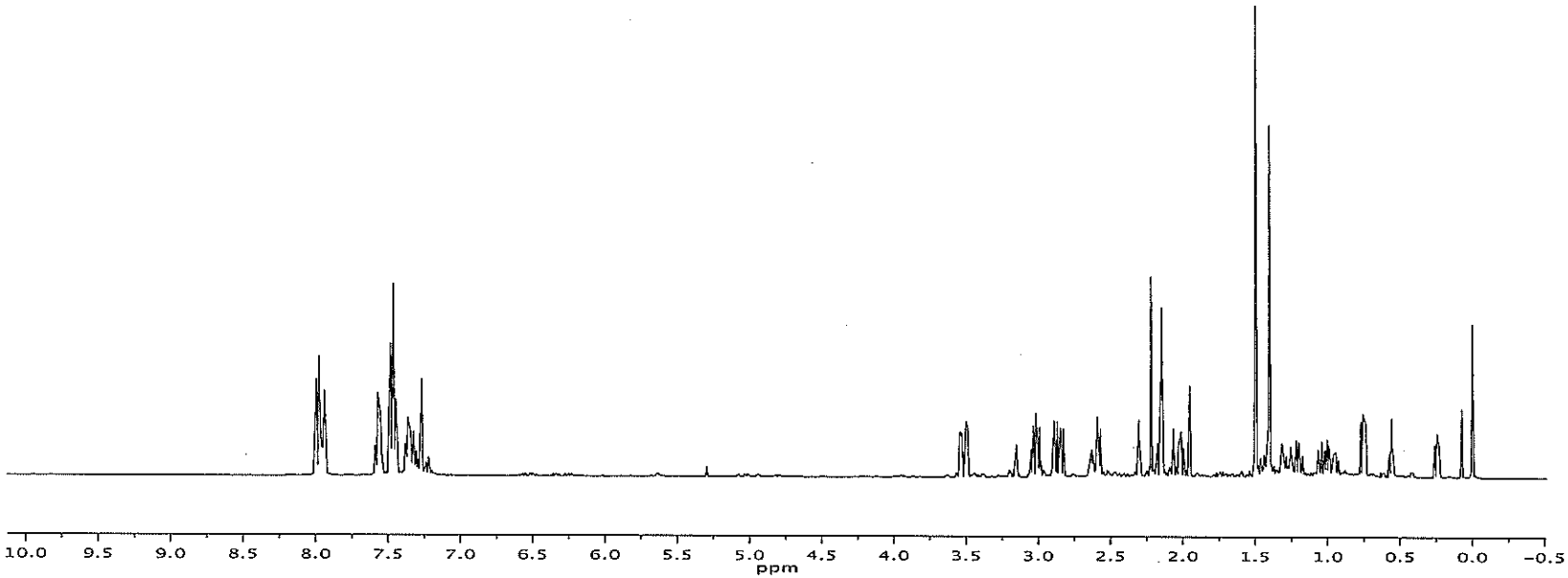

207.4
203.5
136.2
133.2
128.9
128.7
47.1
36.4
30.4
18.0
O
O
24
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

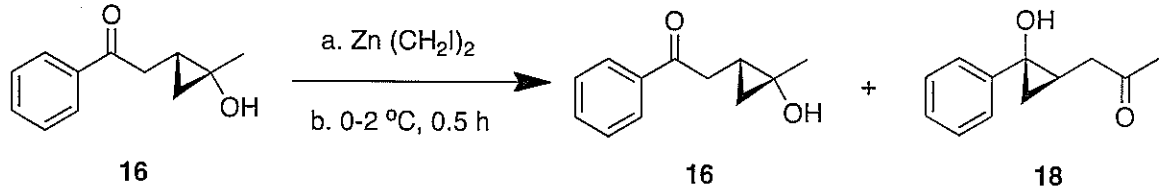


18 **18** **16**

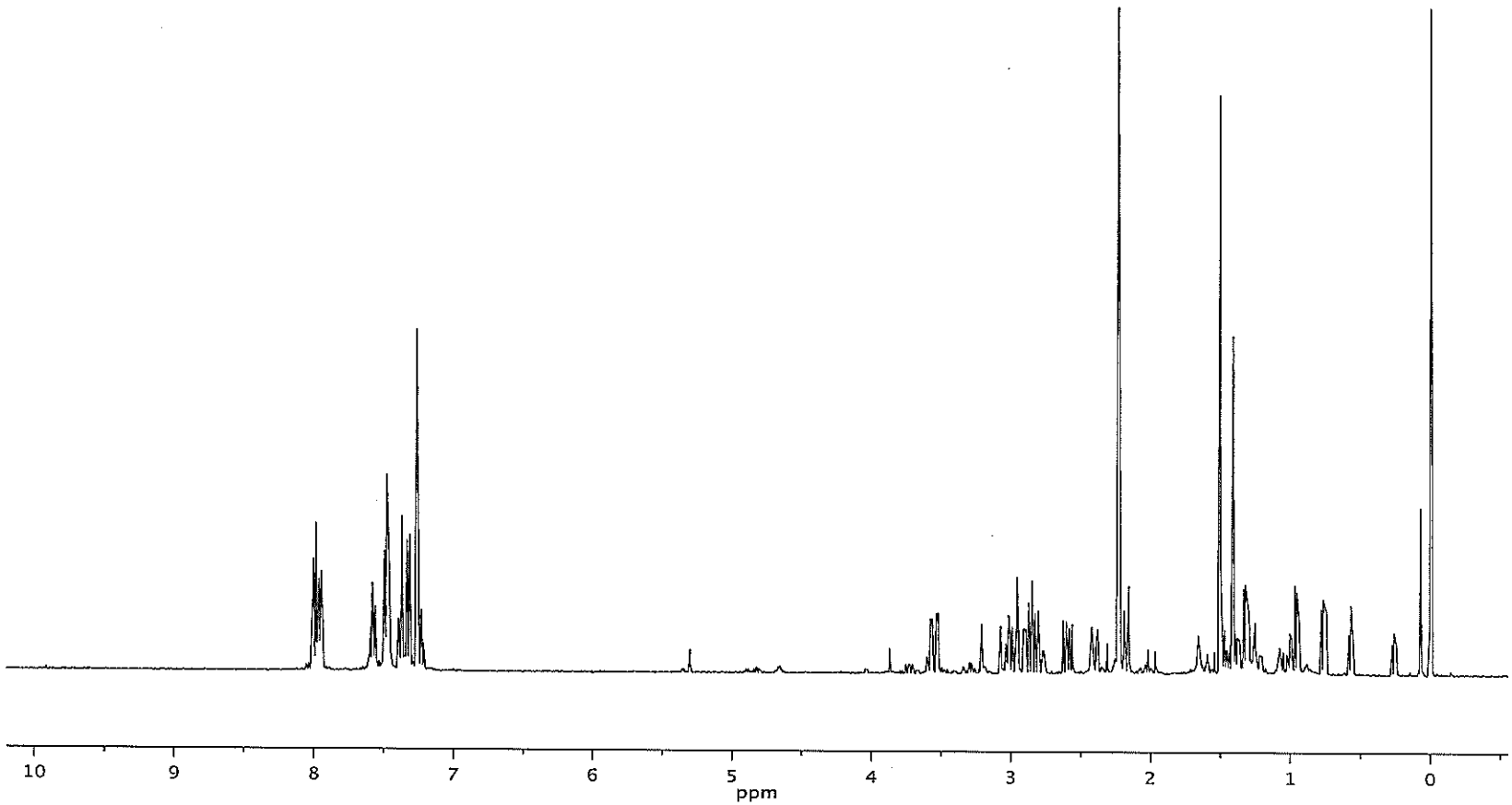


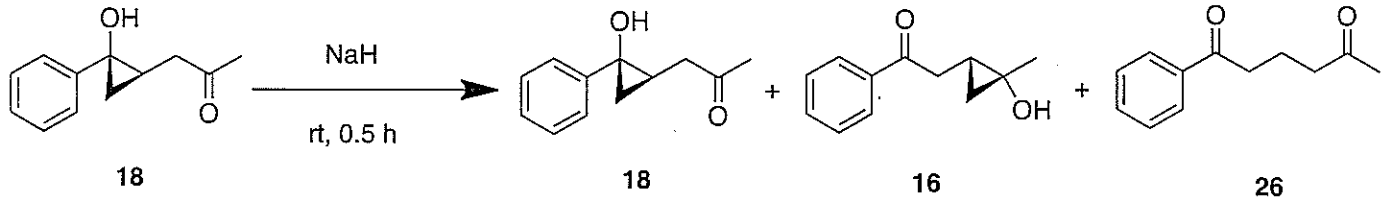

OH
O
18
Et2Zn
rt, 12 h
OH
O
18
24
O
O
16
OH
25
26
+


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

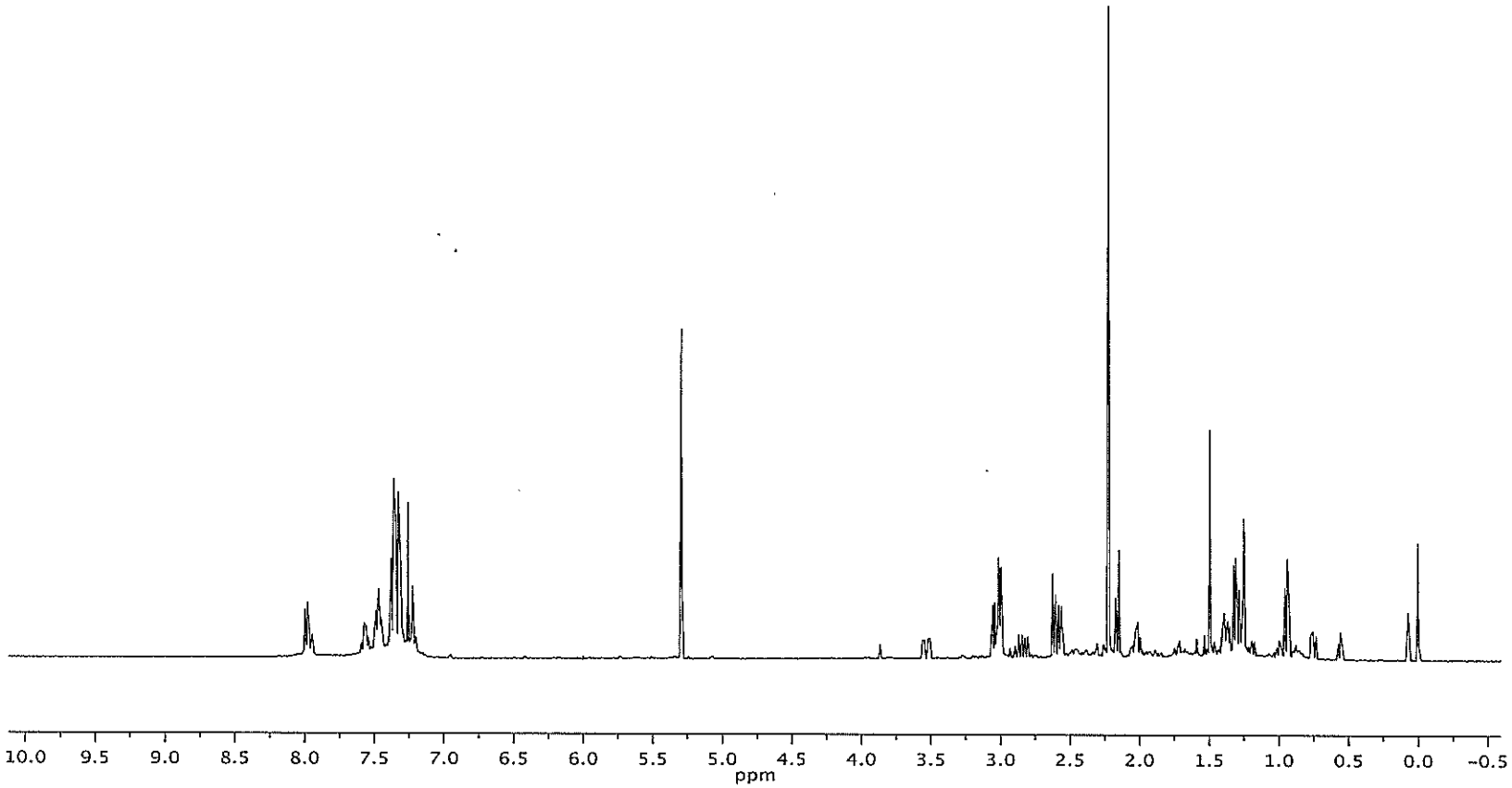


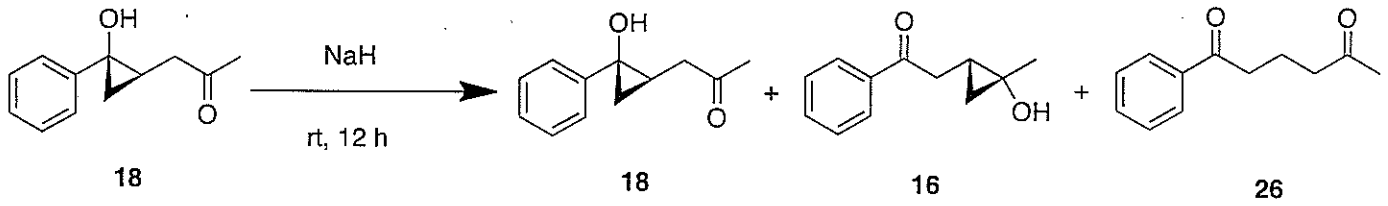
16 **16** **18**



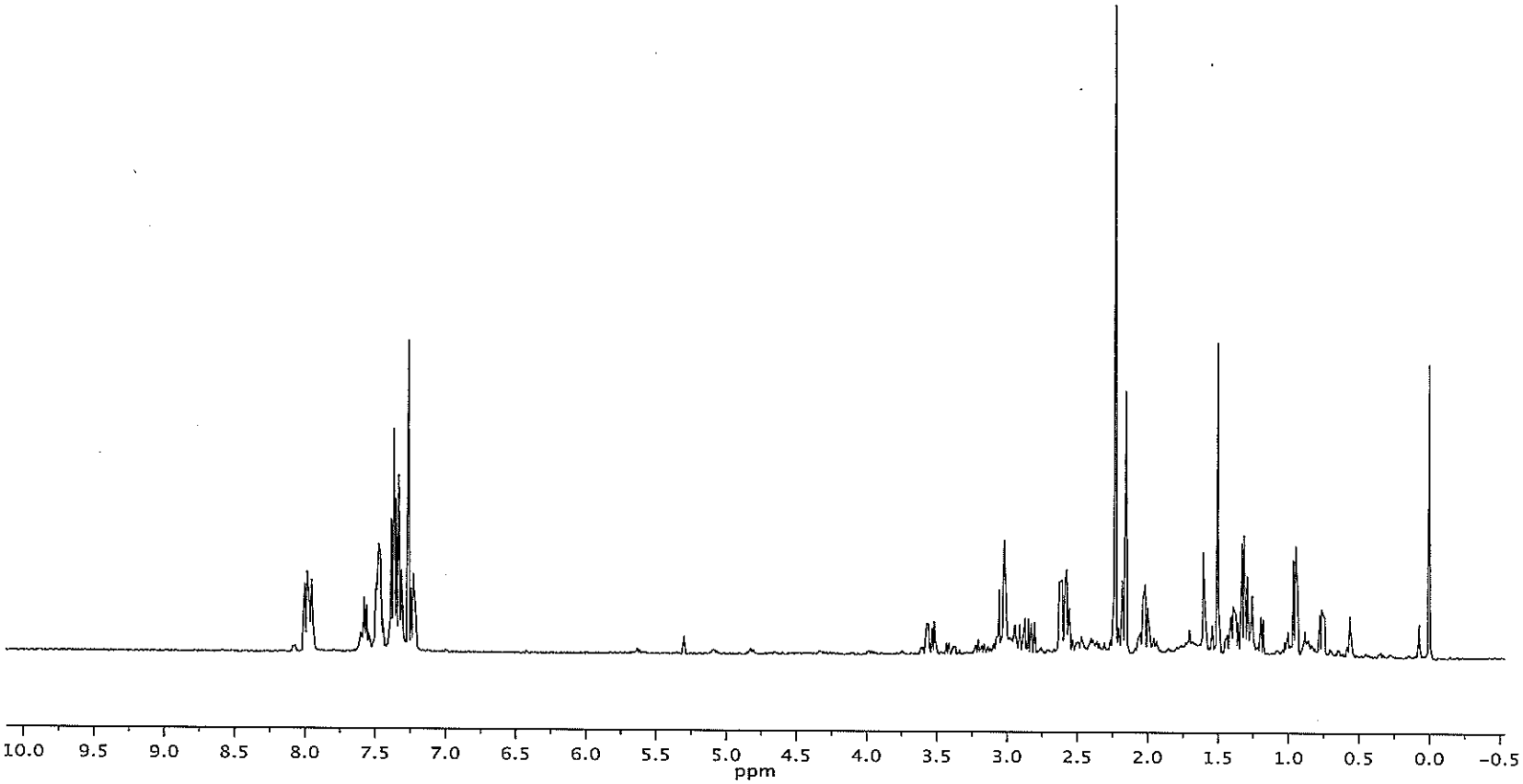

OH
O
NaH
rt, 0.5 h
OH
O
+
O
OH
+
O
O

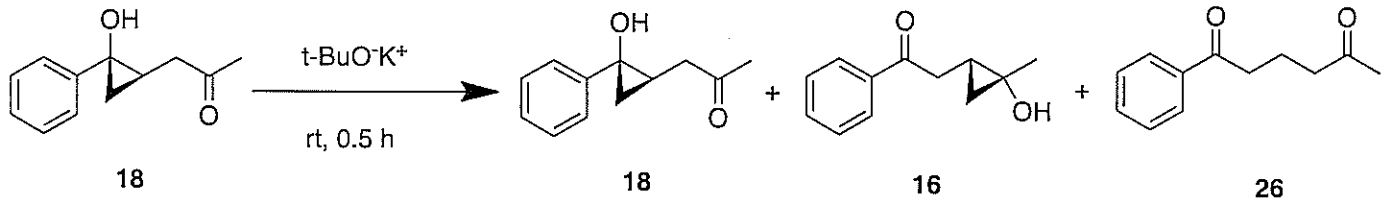
18 18 16 26

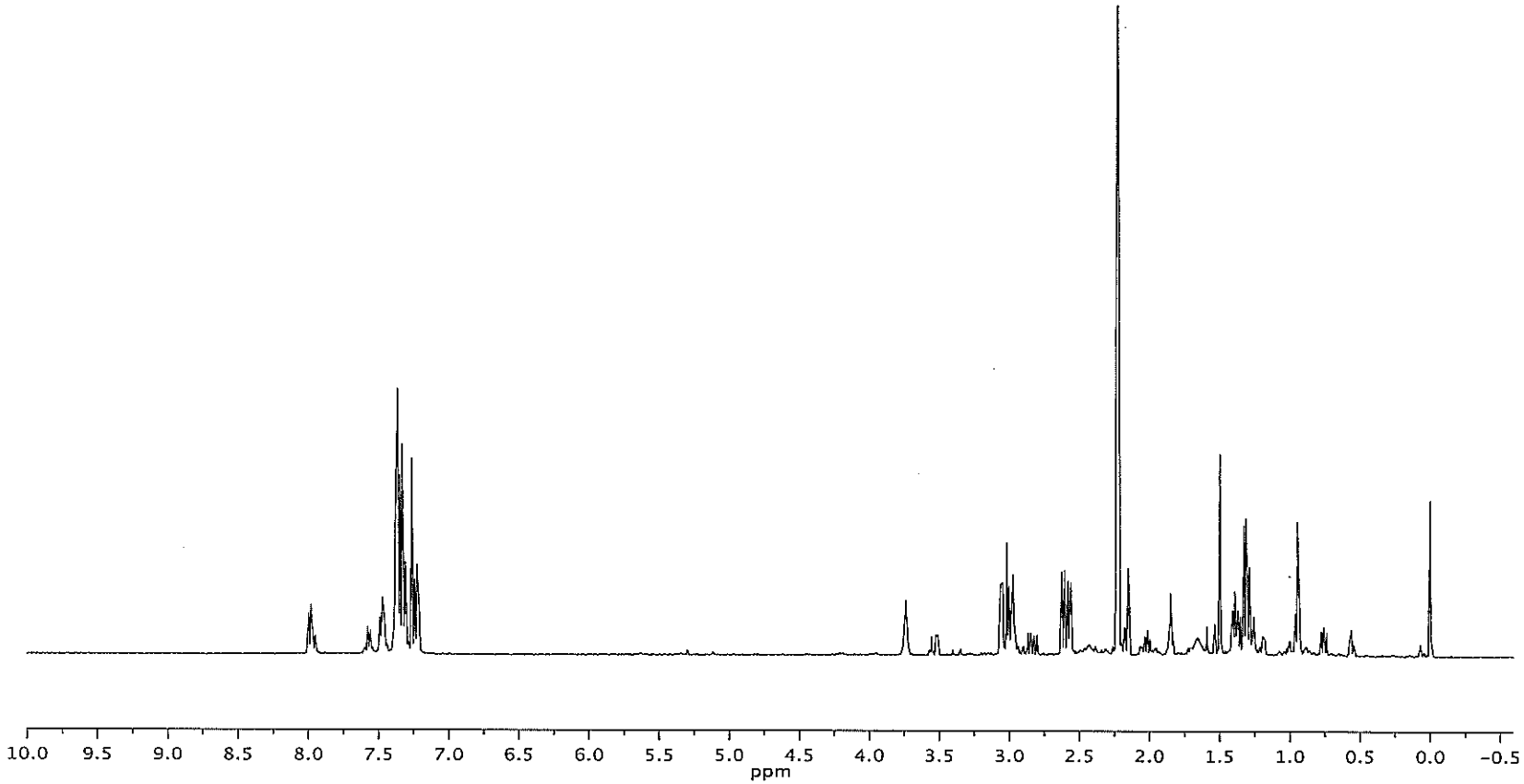

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

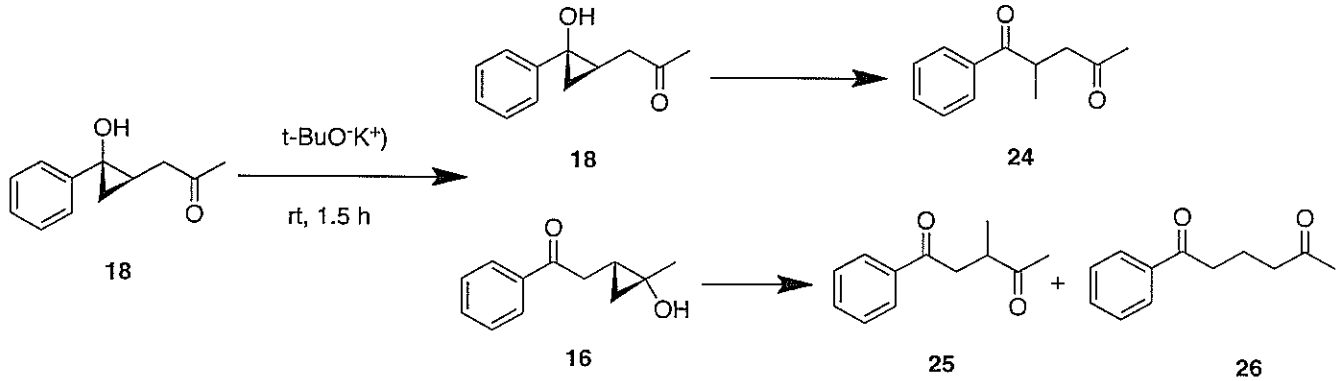

OH
O
NaH
rt, 12 h
OH
O
+
O
OH
+
O
O

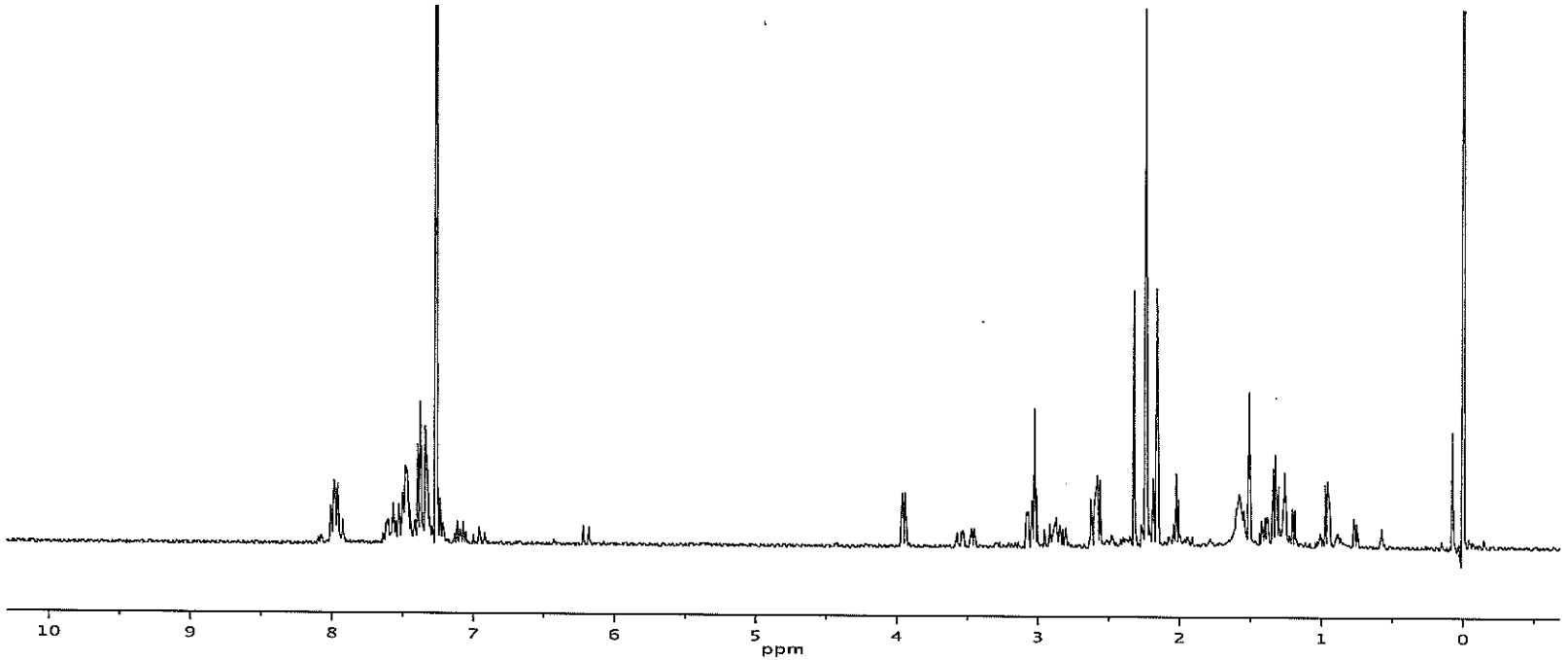
18 18 16 26

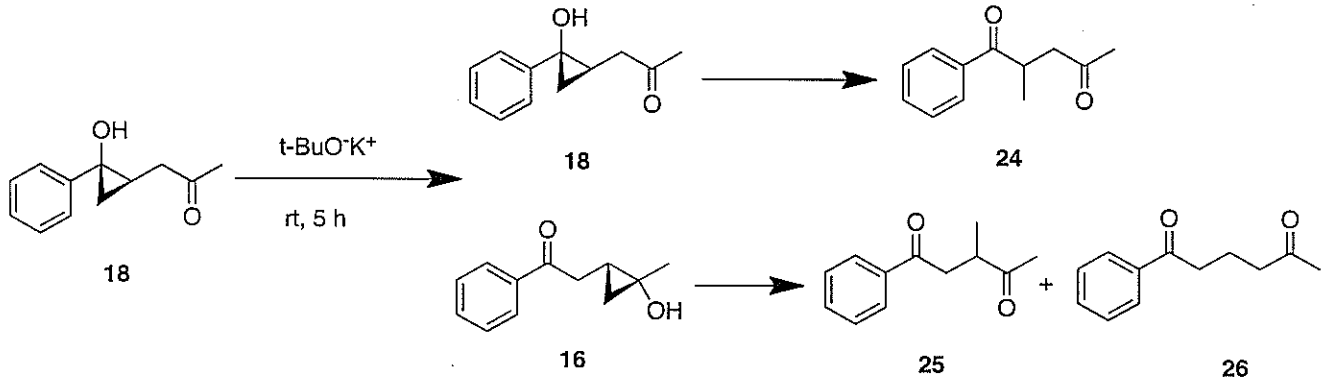

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

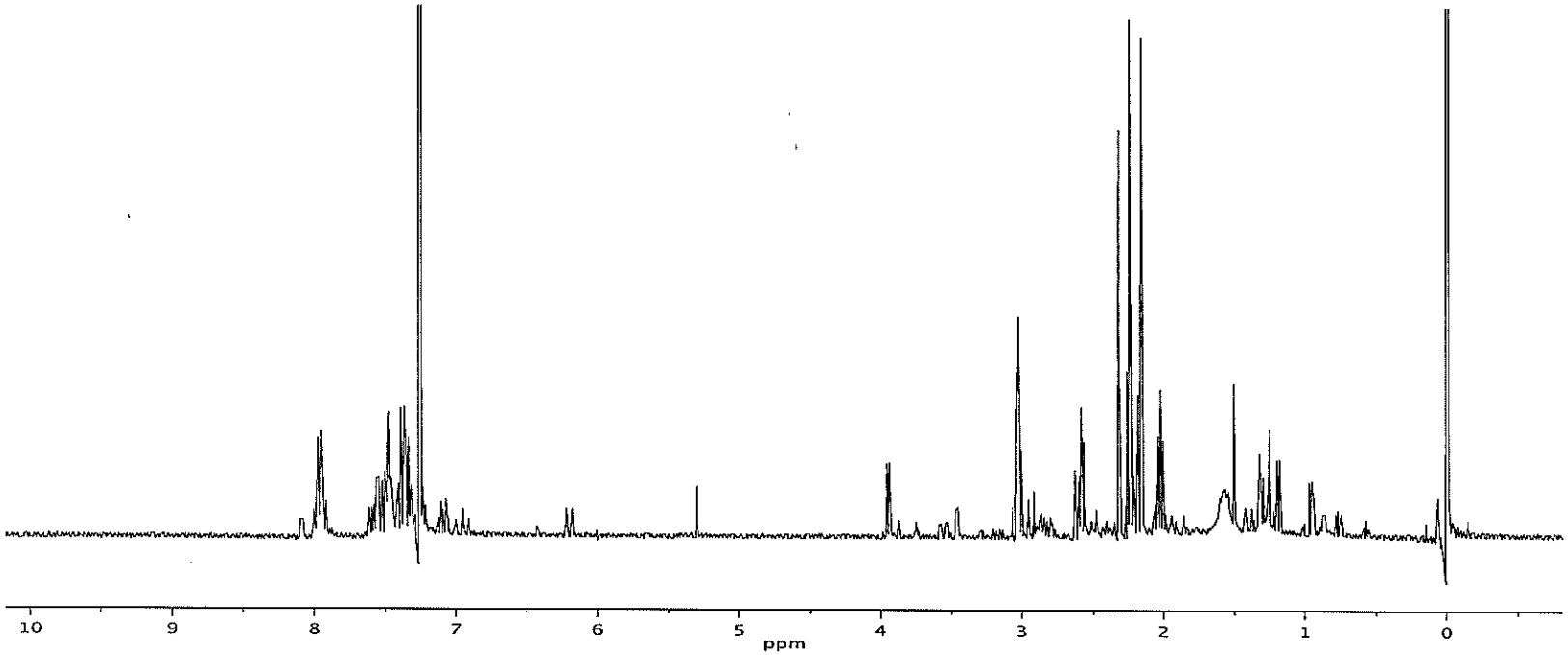

OH
O
t-BuO⁻K⁺
rt, 0.5 h
18
OH
O
18
+
O
OH
16
+
O
O
26

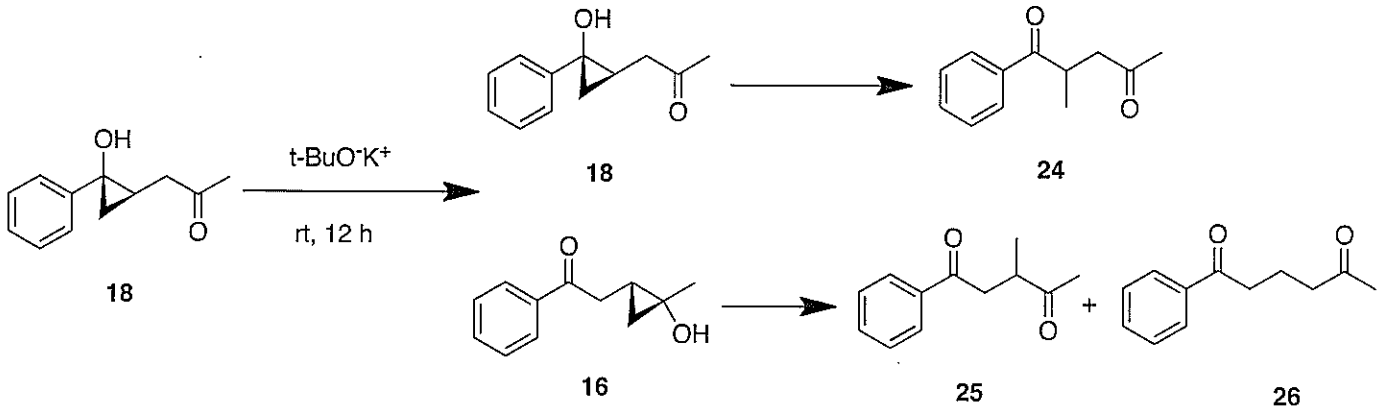

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

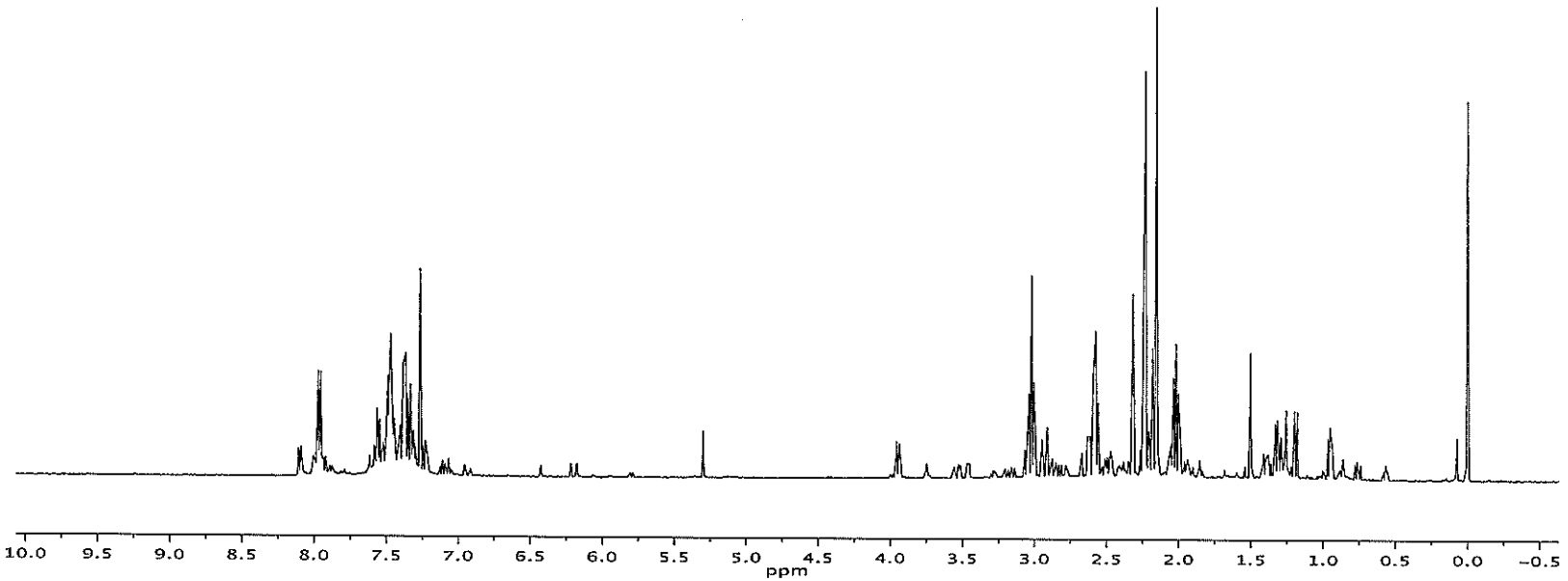

OH
O
t-BuO⁻K⁺)
rt, 1.5 h
18
18
24
16
25
26

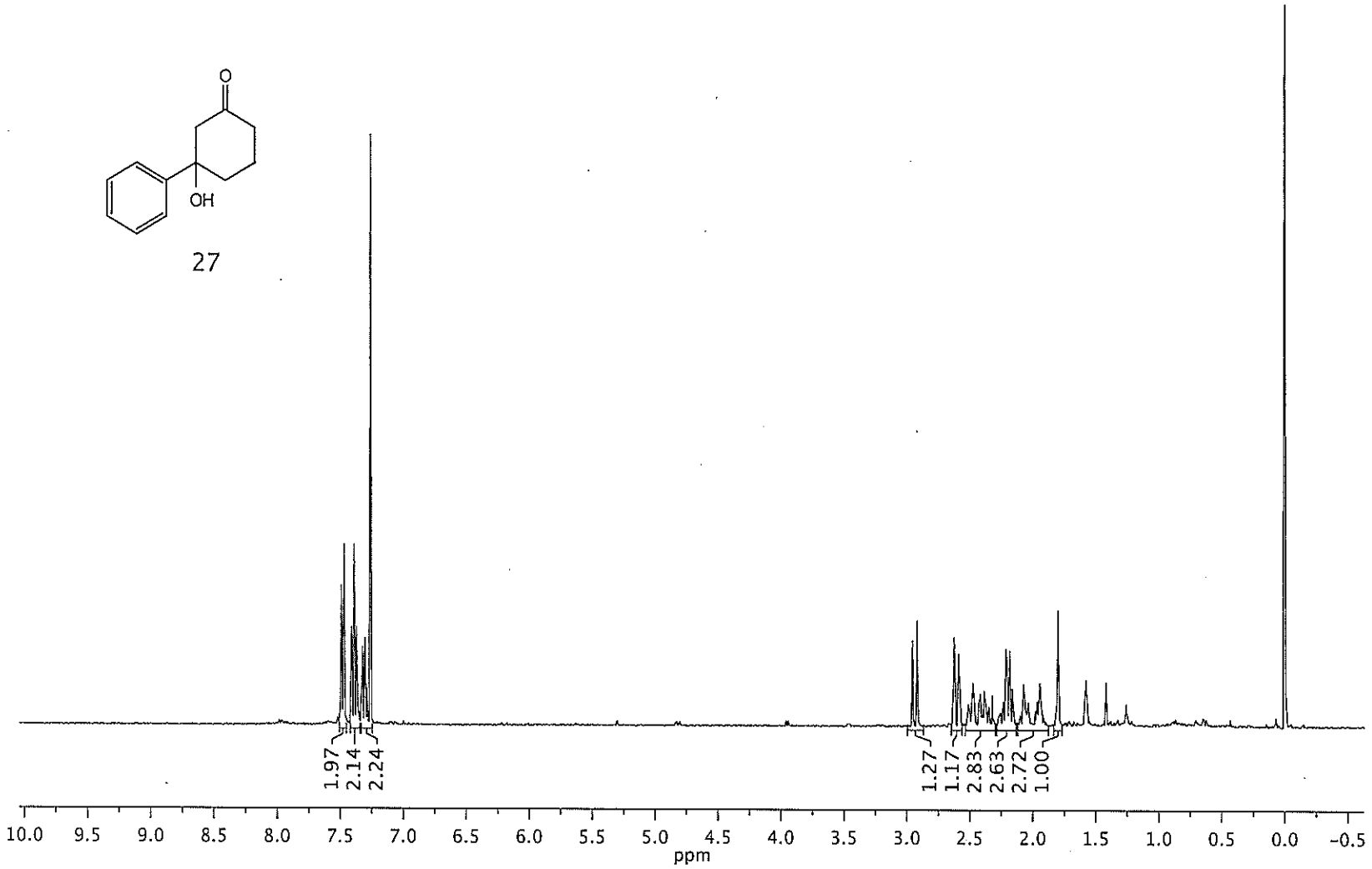

10
9
8
7
6
5
ppm
4
3
2
1
0


OH
O
18
t-BuO⁻K⁺
rt, 5 h
OH
O
18
O
O
24
O
OH
16
O
O
25
+
O
O
26

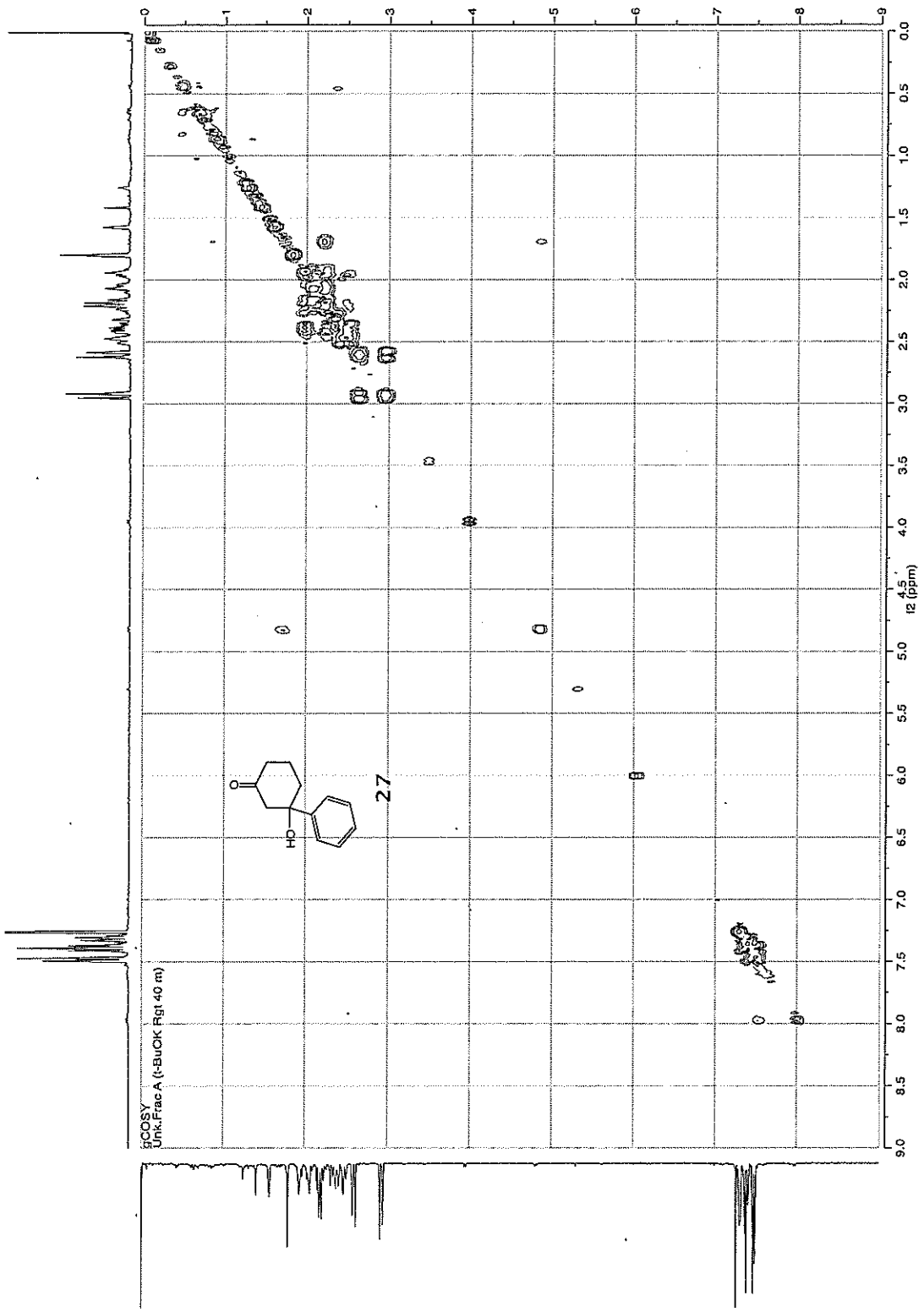

10
9
8
7
6
5
4
3
2
1
0
ppm

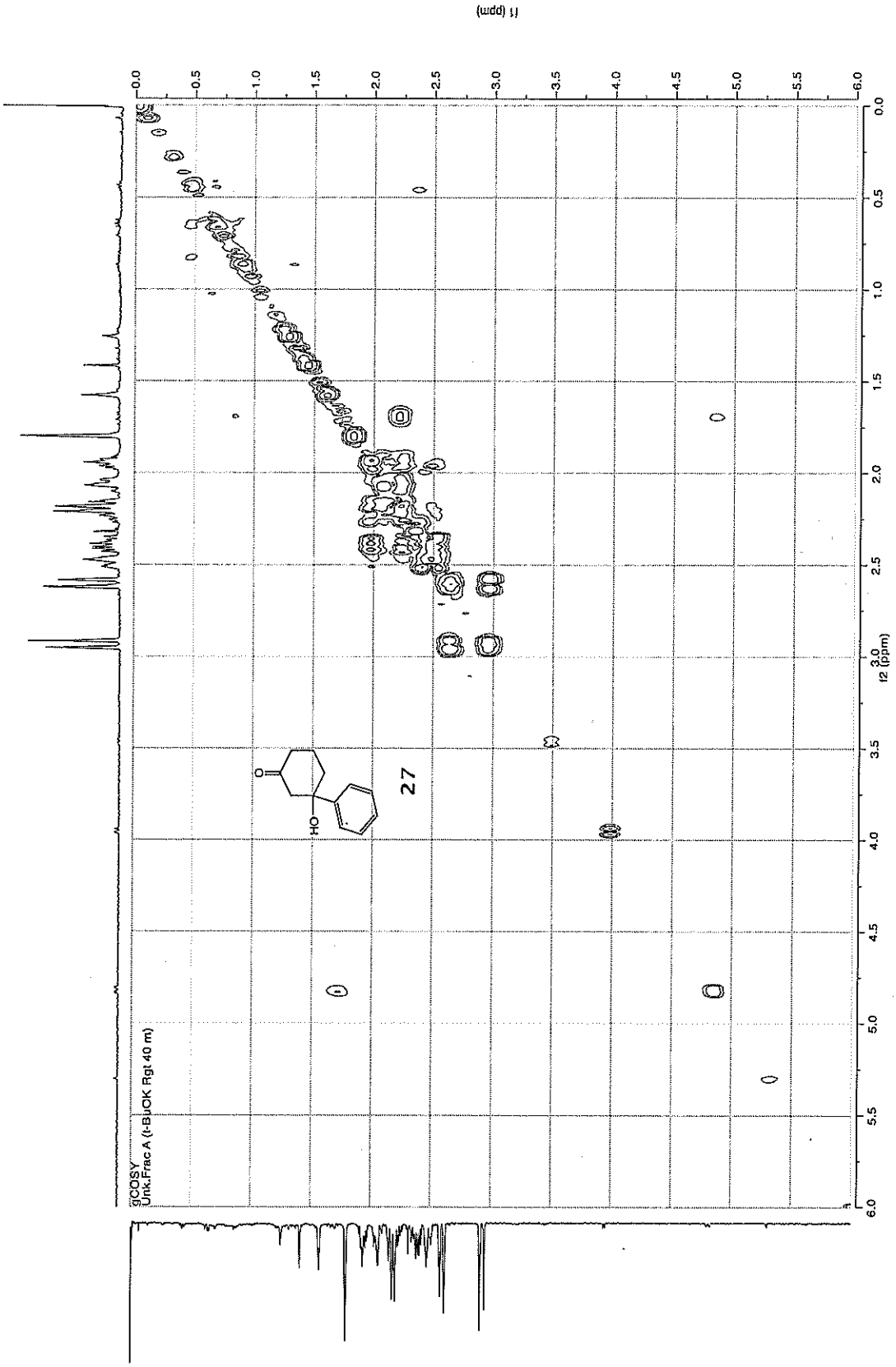

OH
O
t-BuO⁻K⁺
rt, 12 h
18
18
OH
O
24
O
O
16
OH
O
25
O
O
+
26
O
O

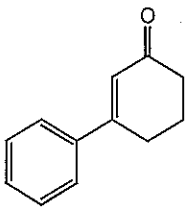

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
ppm


O
OH
27
1.97
2.14
2.24
1.27
1.17
2.83
2.63
2.72
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

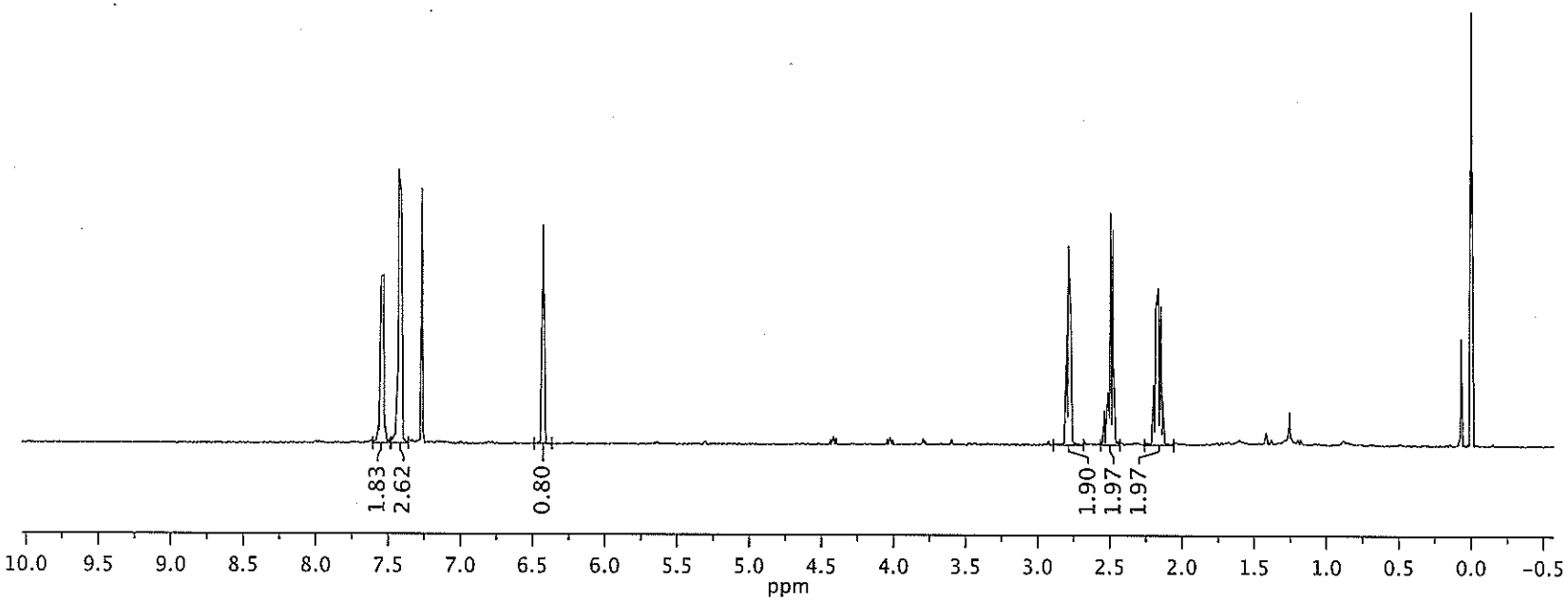
209.9
146.9
146.1
128.9
127.8
124.6
54.6
40.9
38.0
21.7
O
OH
27
ppm

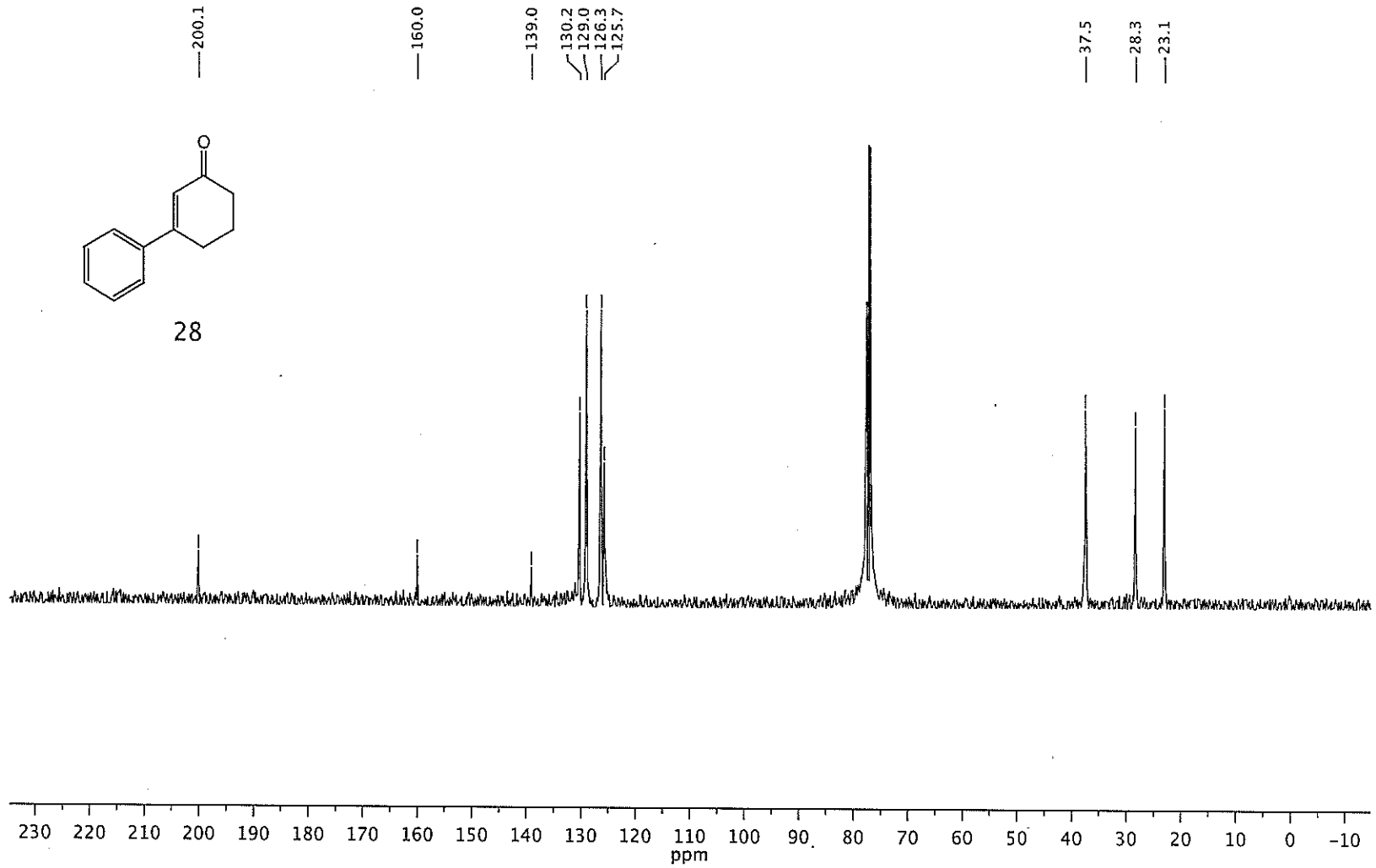

f1 (ppm)
gCOSY
Unk.Frac A (t-BuOK Rgt 40 m)
f2 (ppm)
27
HO
O

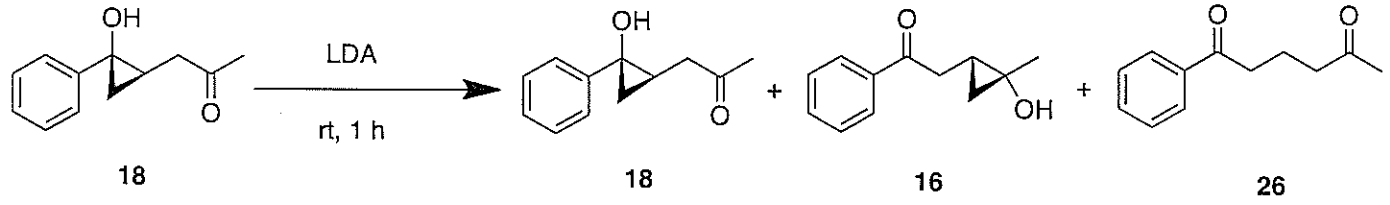

f1 (ppm)
gCOSY
Unk.Frac A (t-BuOK Rgt 40 m)
f2 (ppm)
27
HO
O



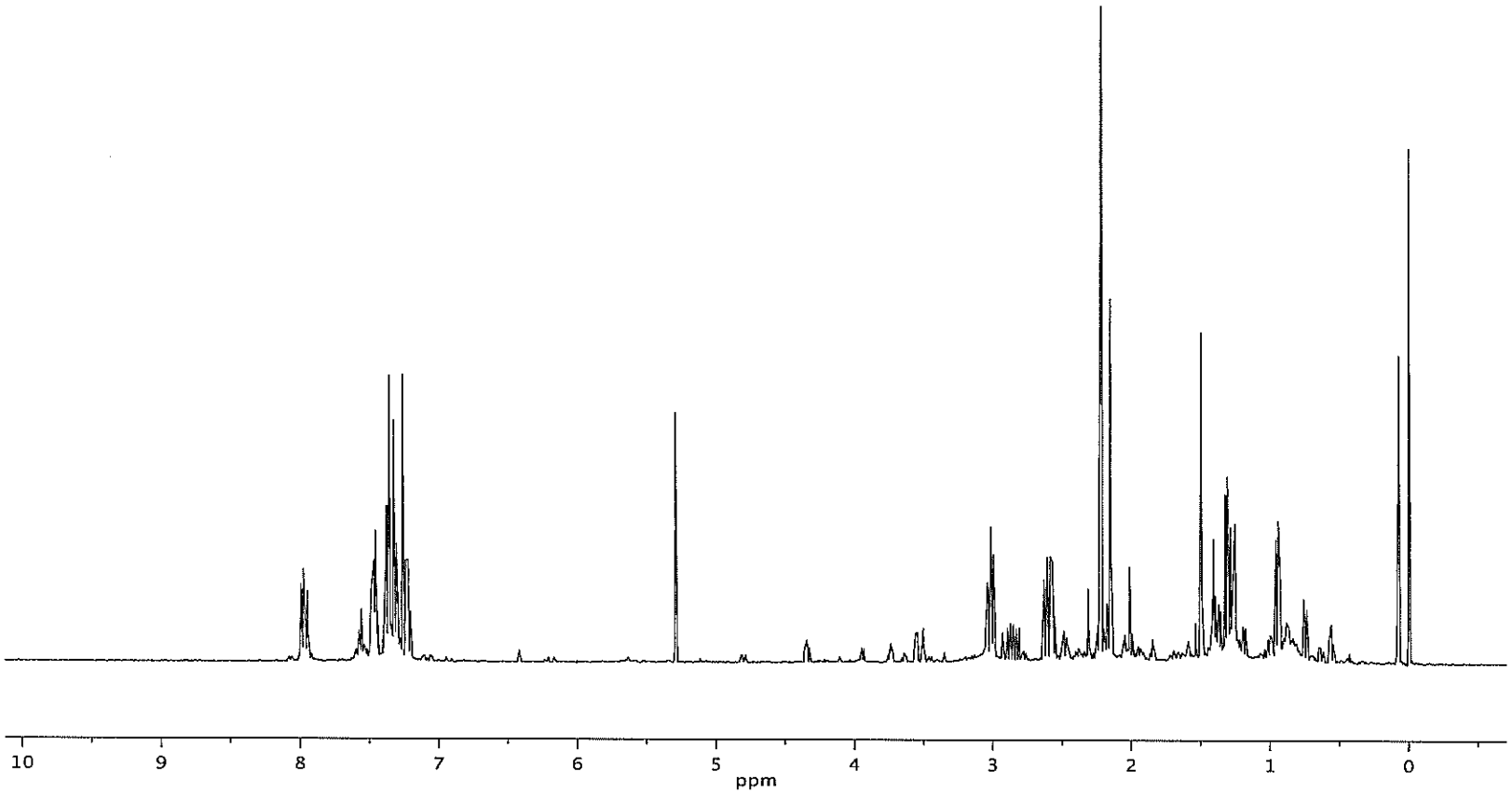
28

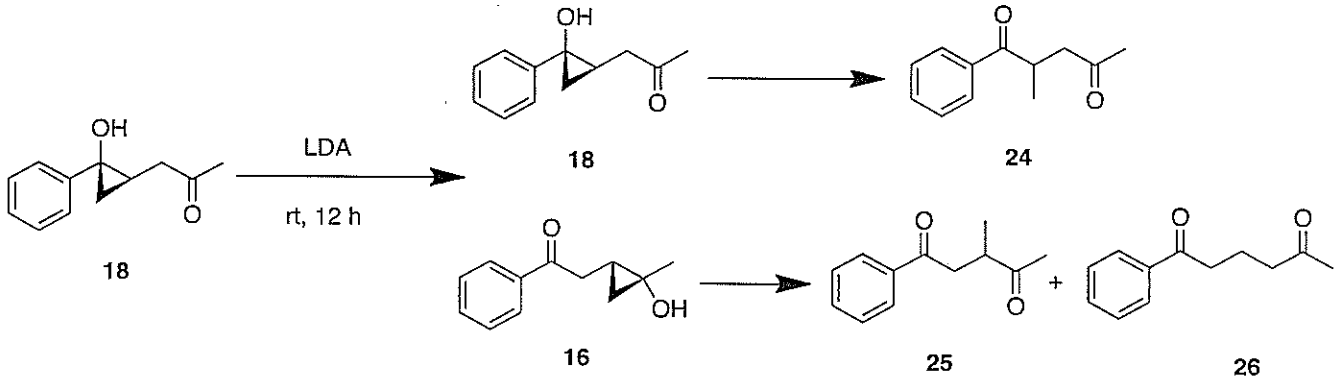

1.83
2.62
0.80
1.90
1.97
1.97
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

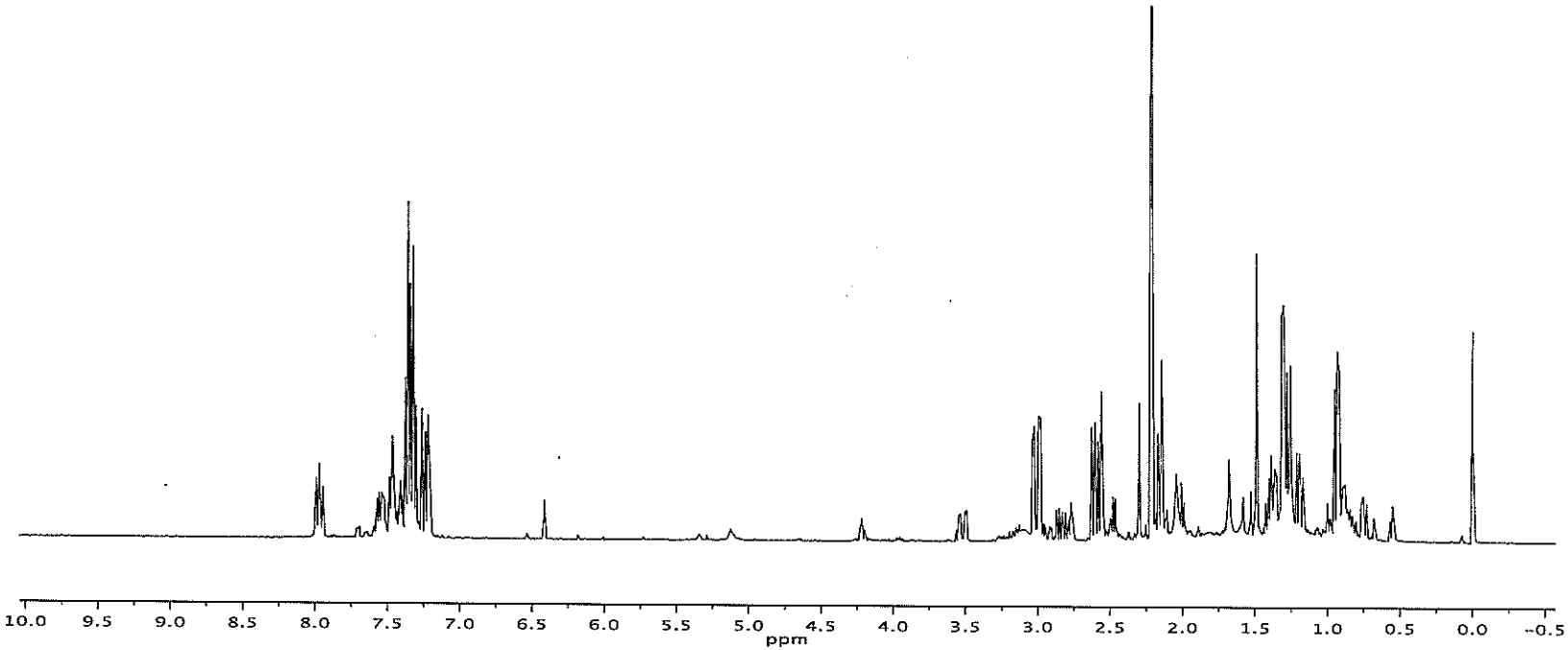

200.1
160.0
139.0
130.2
129.0
126.3
125.7
37.5
28.3
23.1
O
28
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

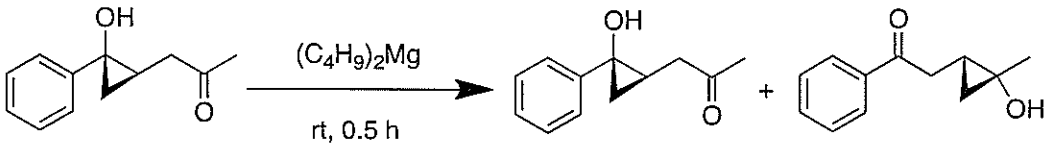


18 18 16 26

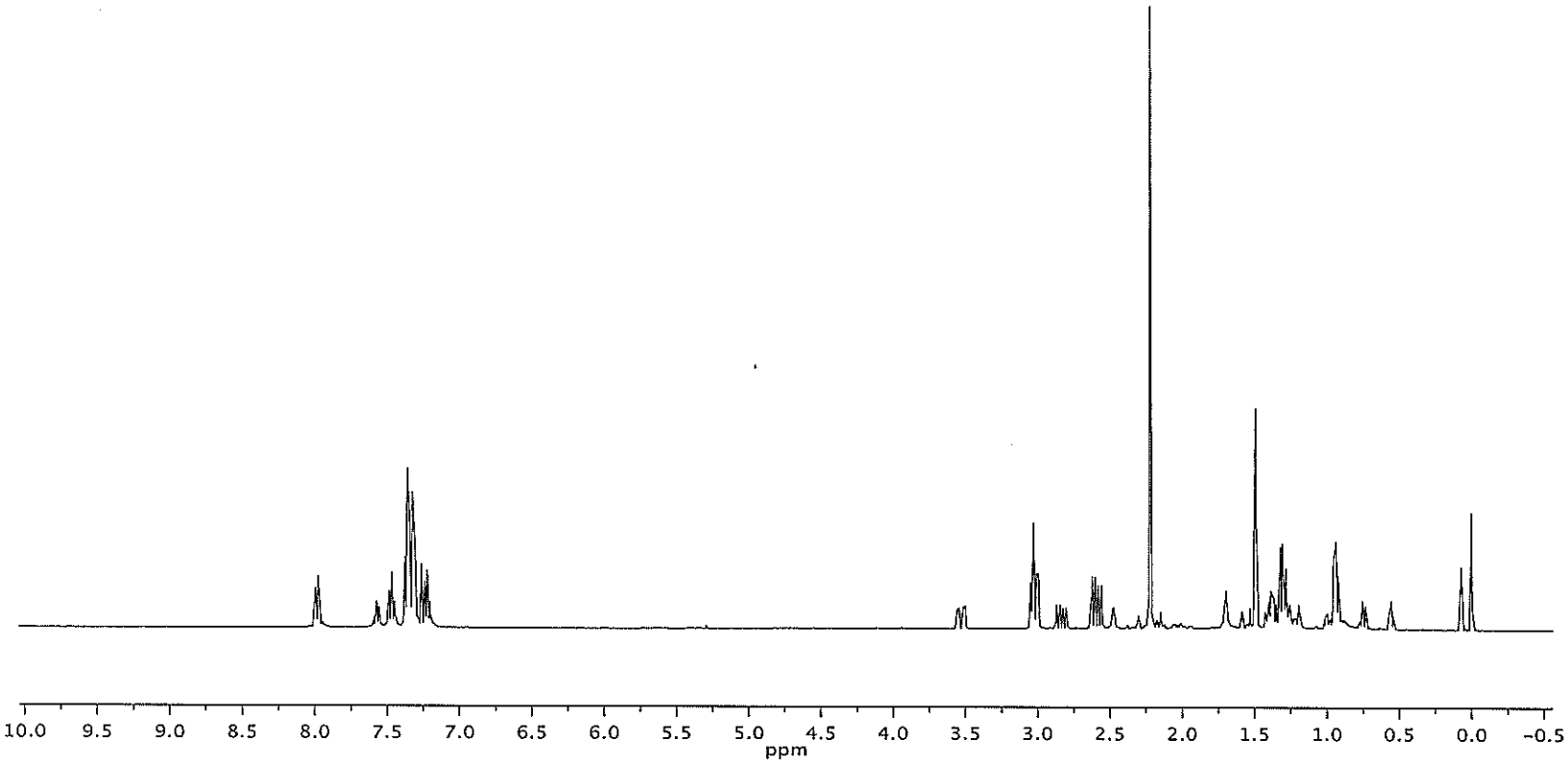


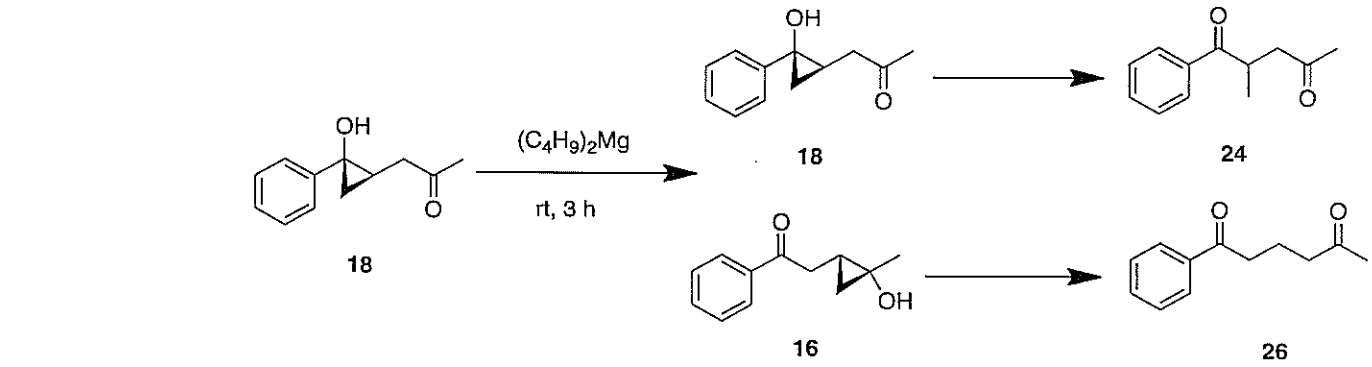

OH
O
LDA
rt, 12 h
18
18
24
16
25
26
+

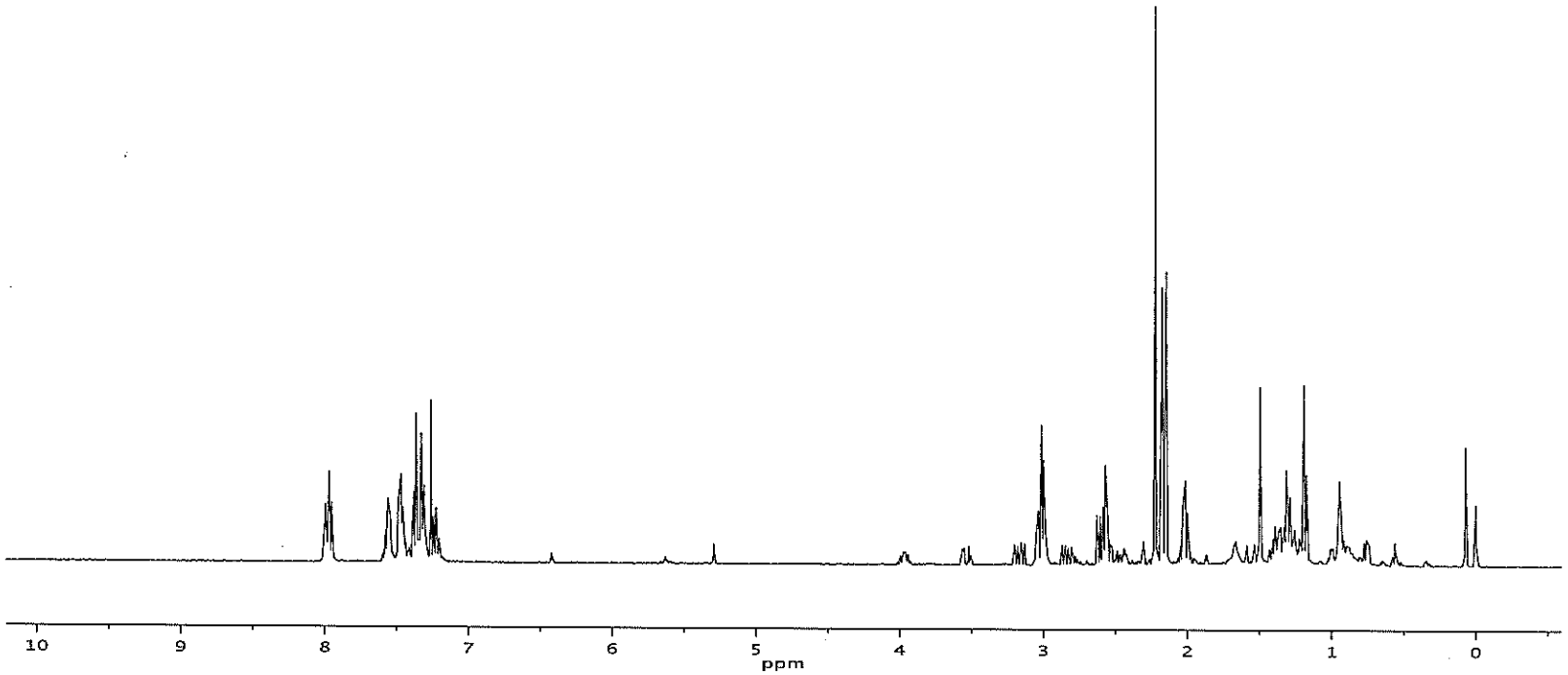

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

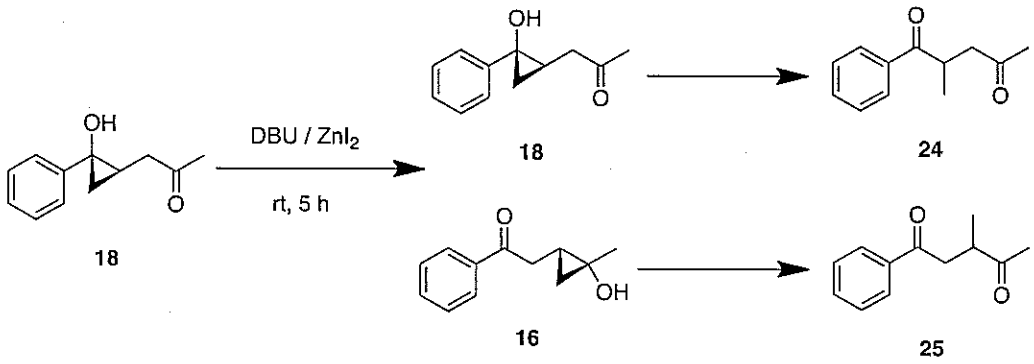

OH
O
$(C_4H_9)_2Mg$
rt, 0.5 h
OH
O
+
O
OH

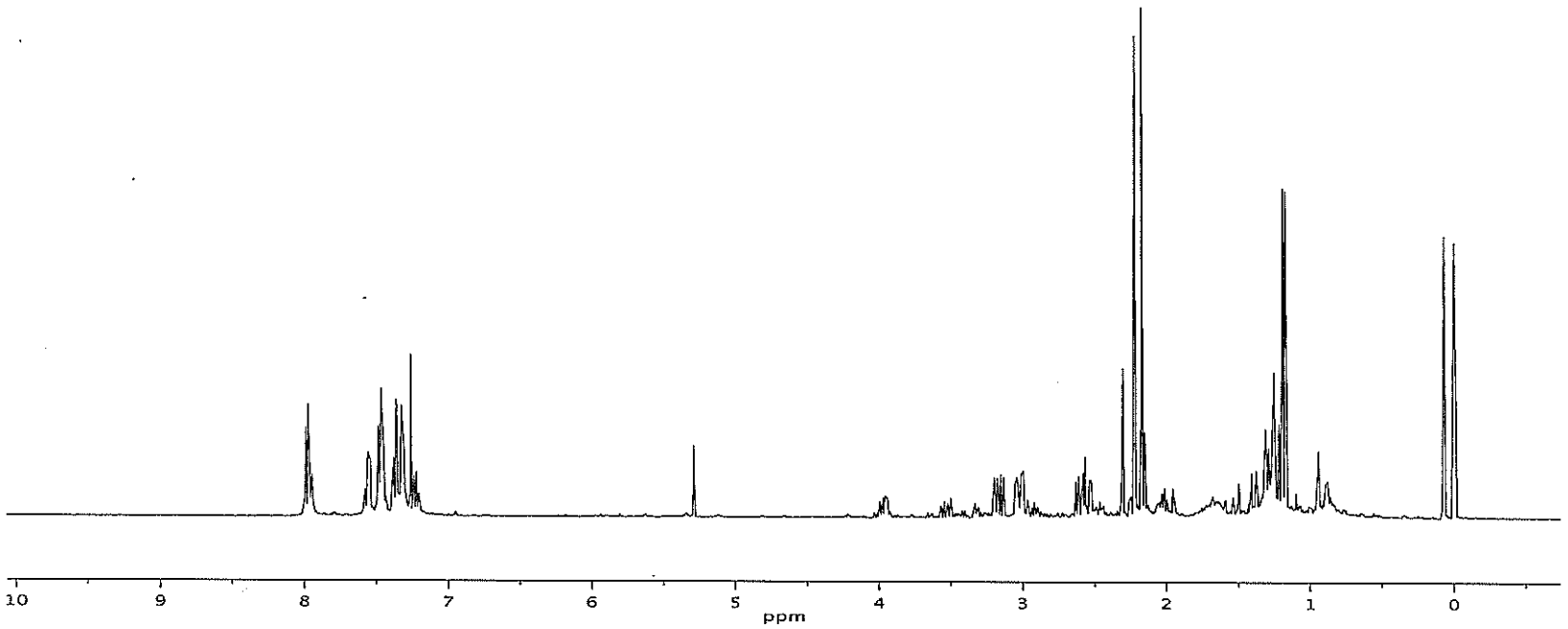
18 **18** **16**

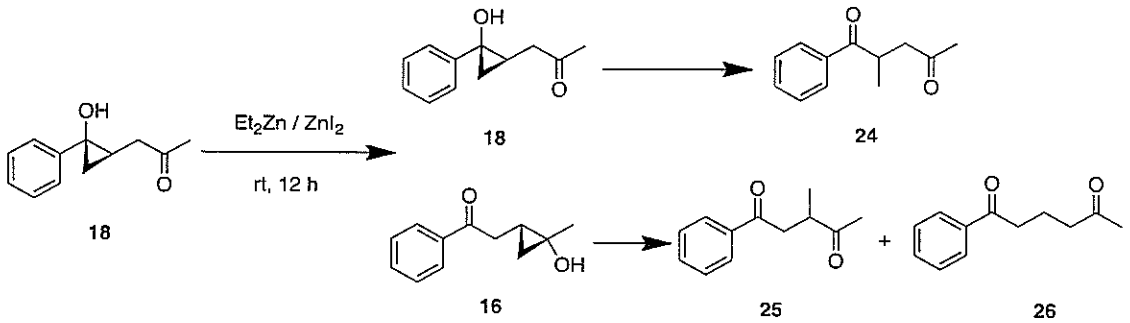

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

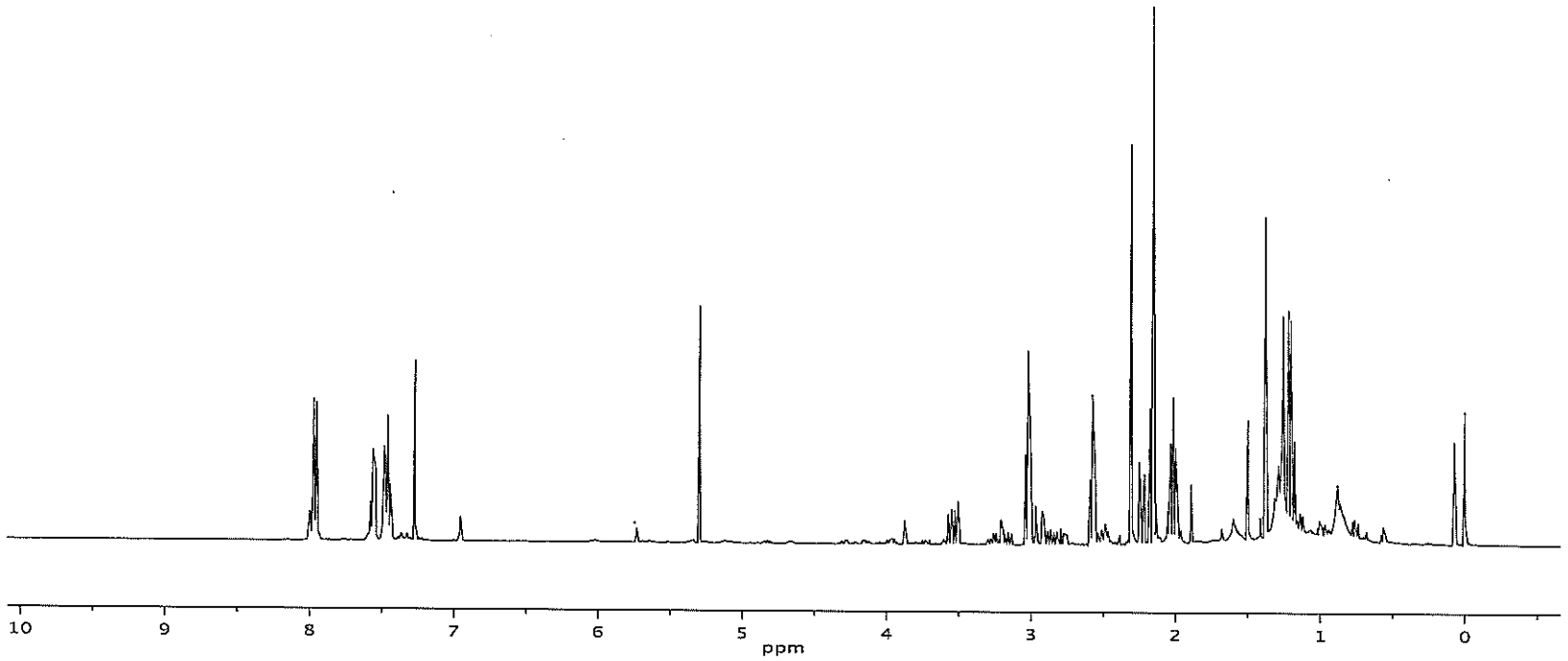

OH
O
18
$(C_4H_9)_2Mg$
rt, 3 h
OH
O
18
O
24
O
OH
16
O
O
26

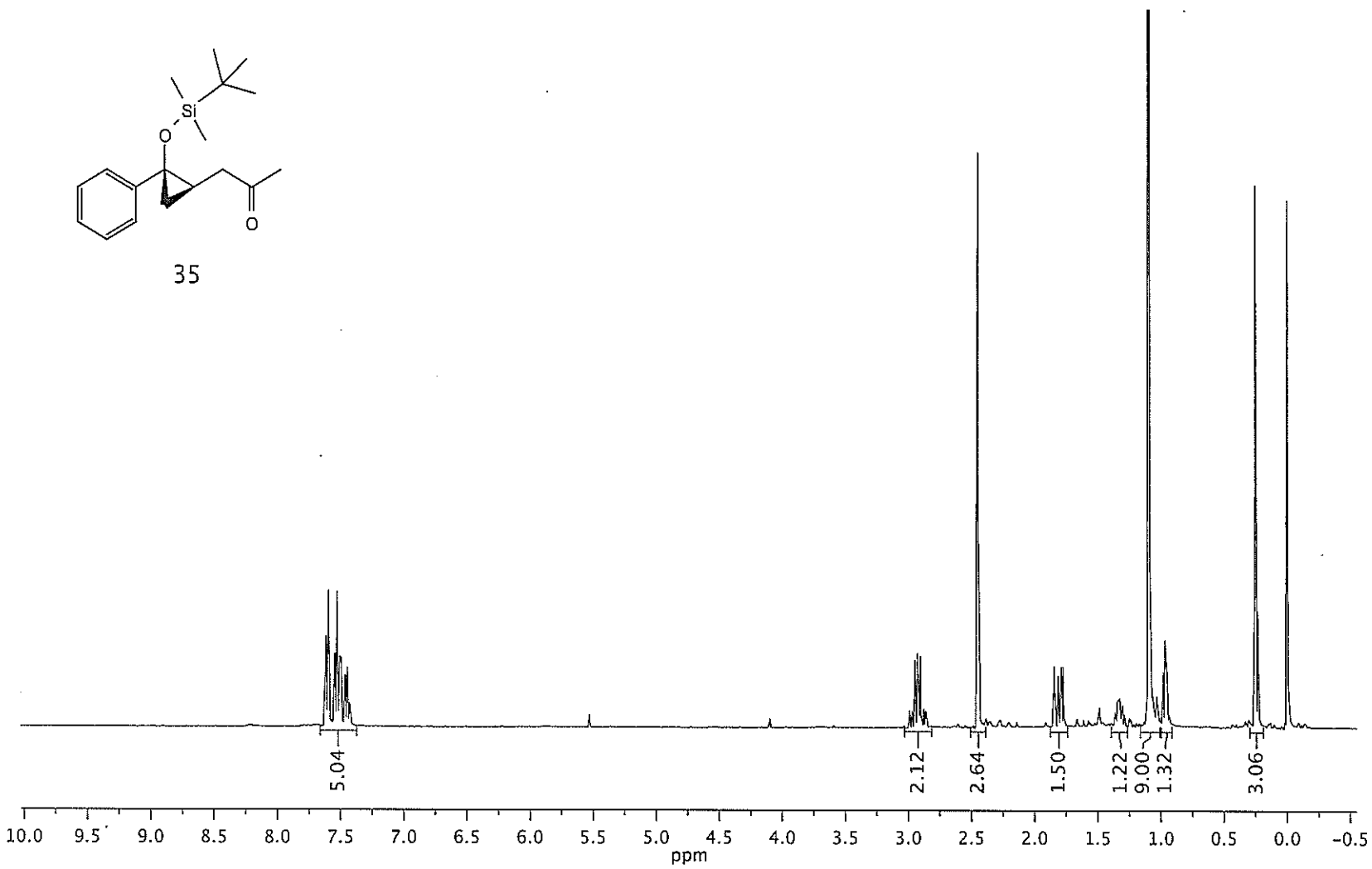

10
9
8
7
6
5
ppm
4
3
2
1
0

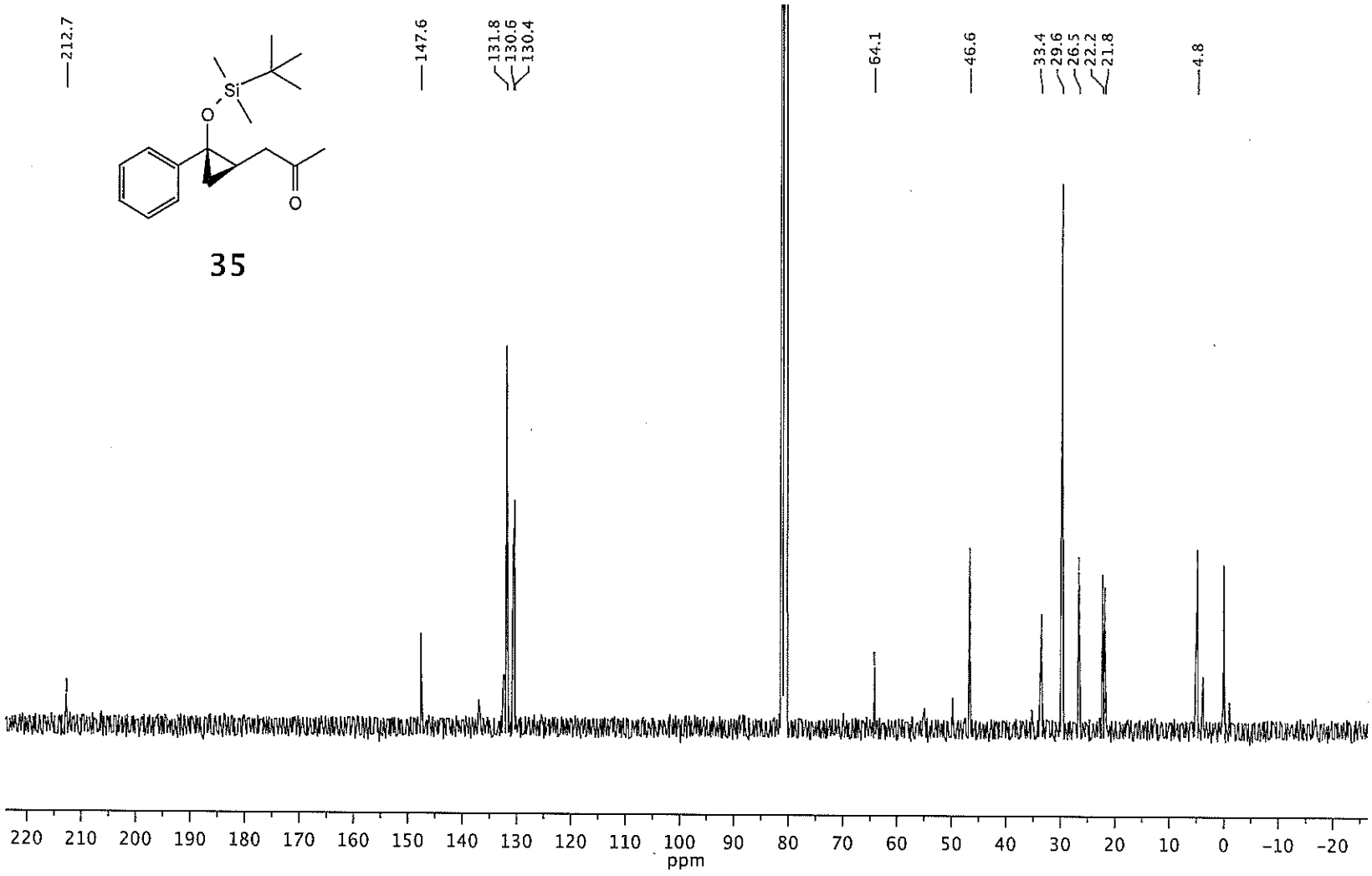

OH
O
DBU / ZnI2
rt, 5 h
18
OH
O
18
O
O
24
O
OH
16
O
O
25


10
9
8
7
6
5
4
3
2
1
0
ppm

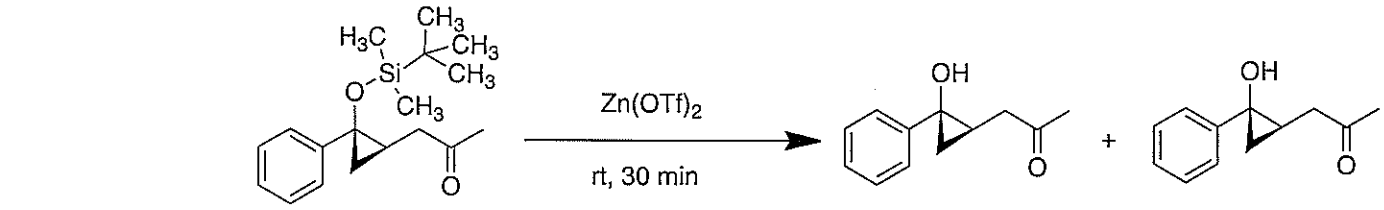

OH
O
18
Et2Zn / ZnI2
rt, 12 h
OH
O
18
24
O
OH
16
O
O
25
+
O
O
26


10
9
8
7
6
5
ppm
4
3
2
1
0

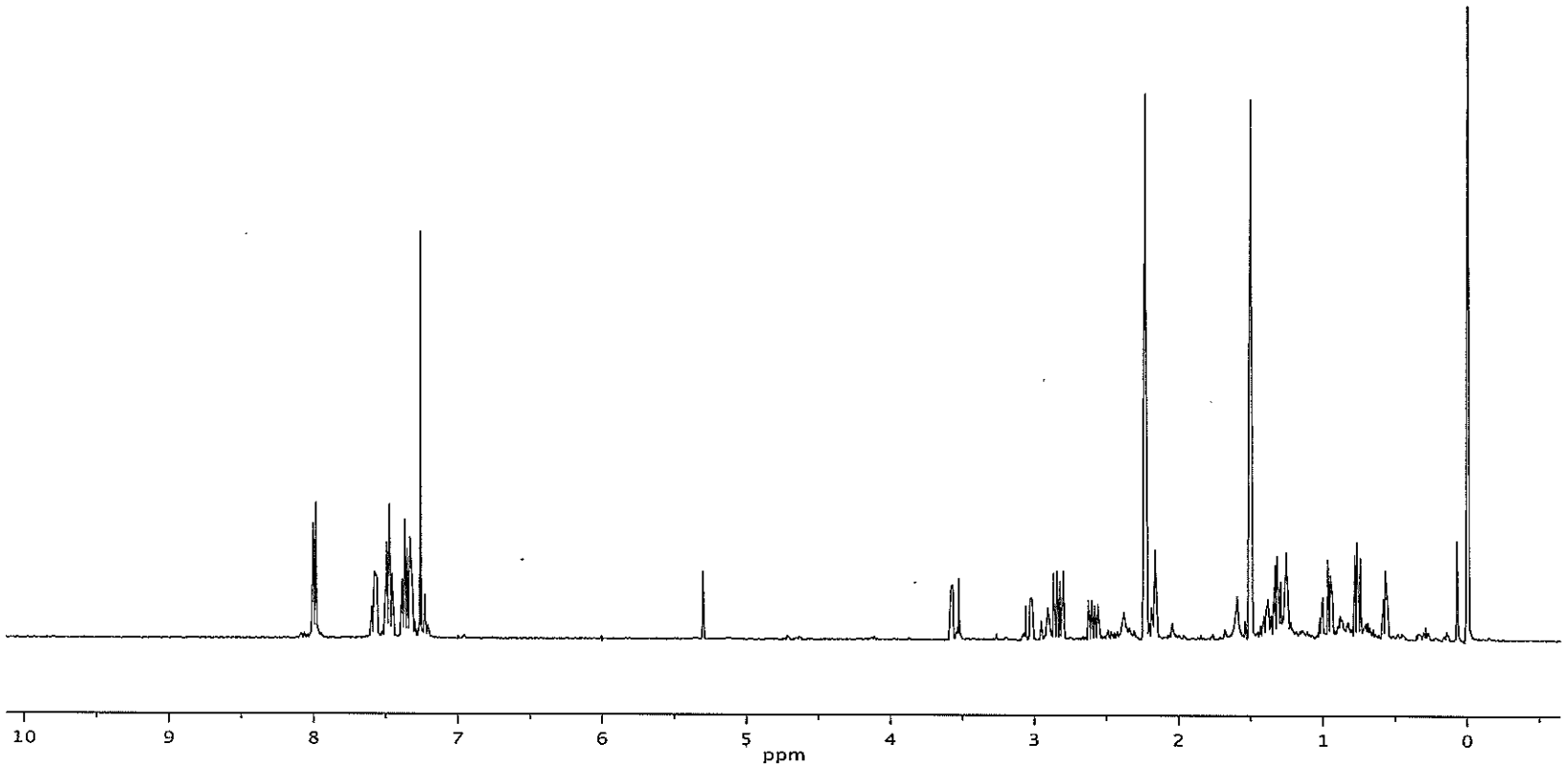

Si
O
O
35
5.04
2.12
2.64
1.50
1.22
9.00
1.32
3.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

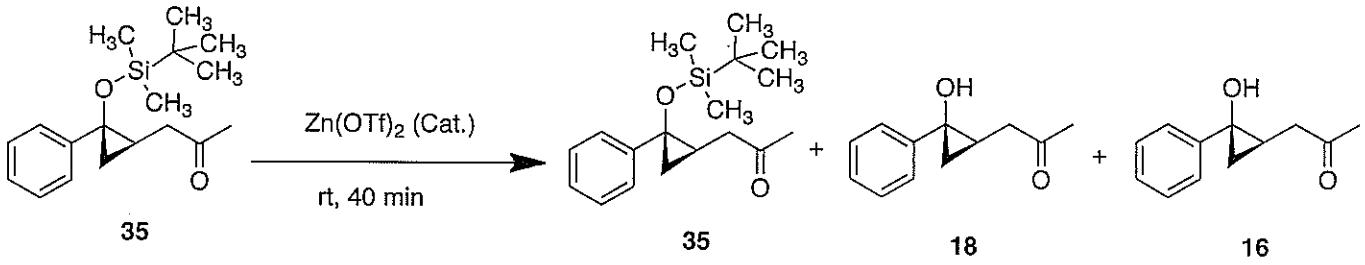

212.7
147.6
131.8
130.6
130.4
64.1
46.6
33.4
29.6
26.5
22.2
21.8
4.8
Si
O
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
ppm

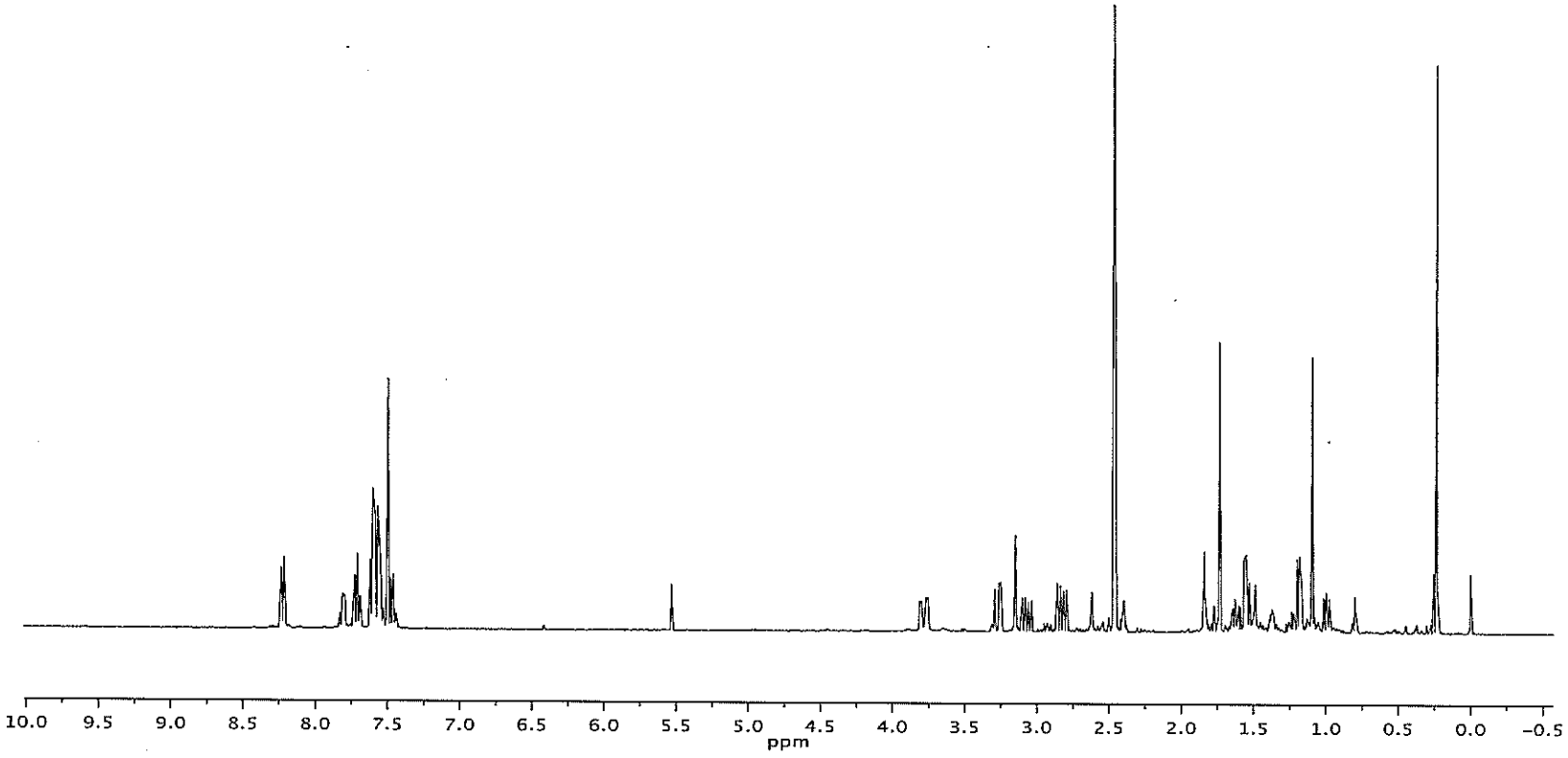
35

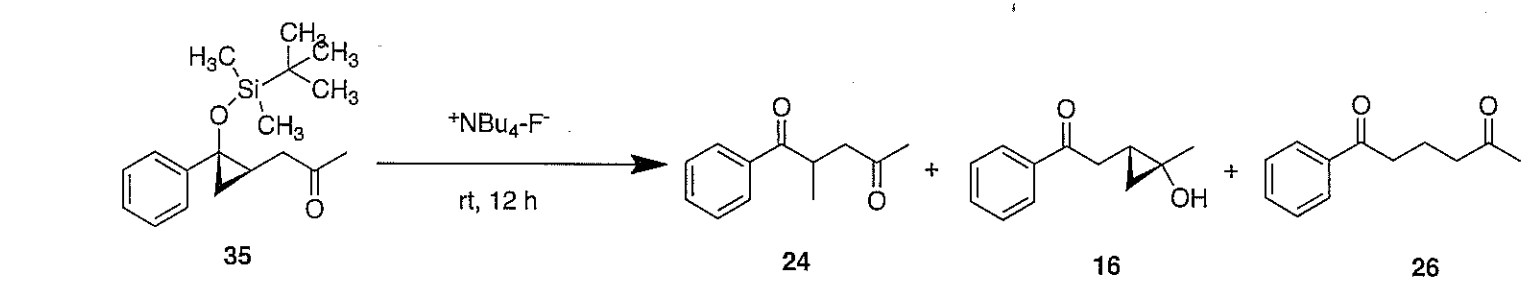

CH3
H3C
CH3
Si
O
CH3
O
Zn(OTf)2
rt, 30 min
OH
O
+
OH
O

35 18 16

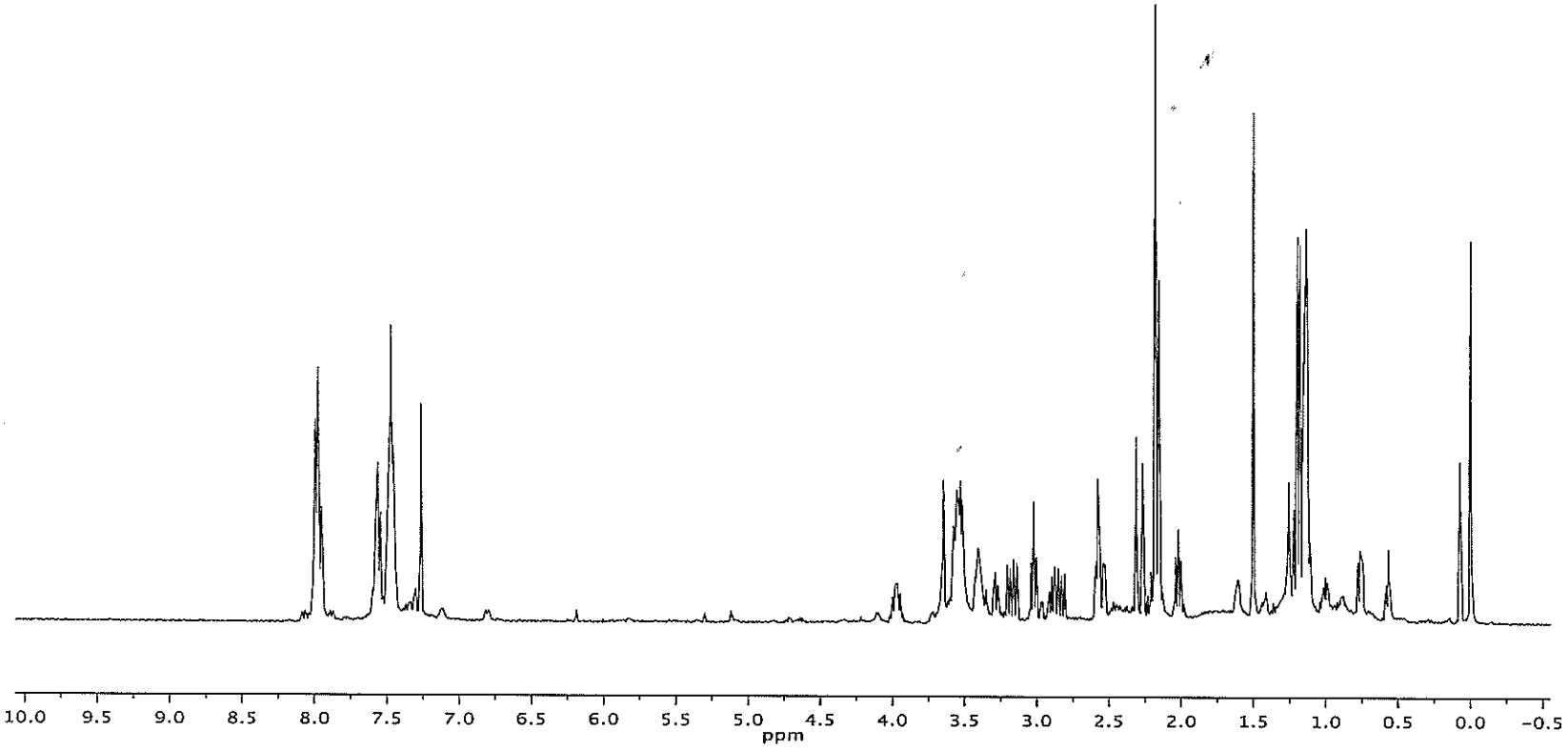

10
9
8
7
6
5
4
3
2
1
0
ppm

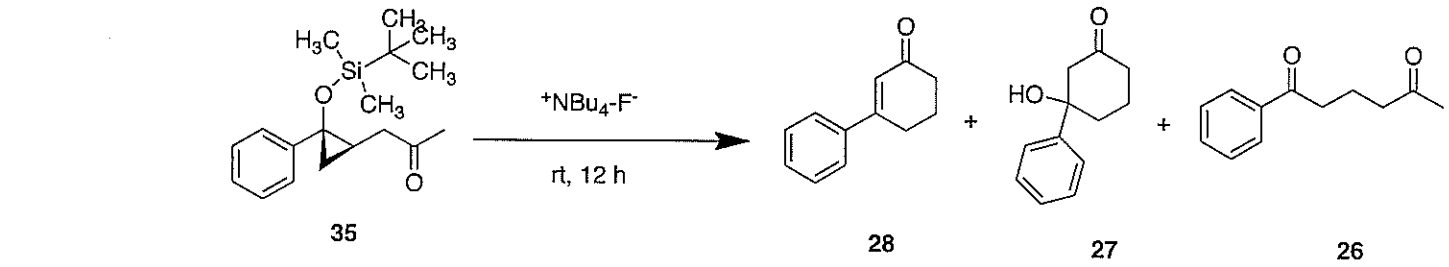

Zn(OTf)2 (Cat.)
rt, 40 min
35
35
18
16


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

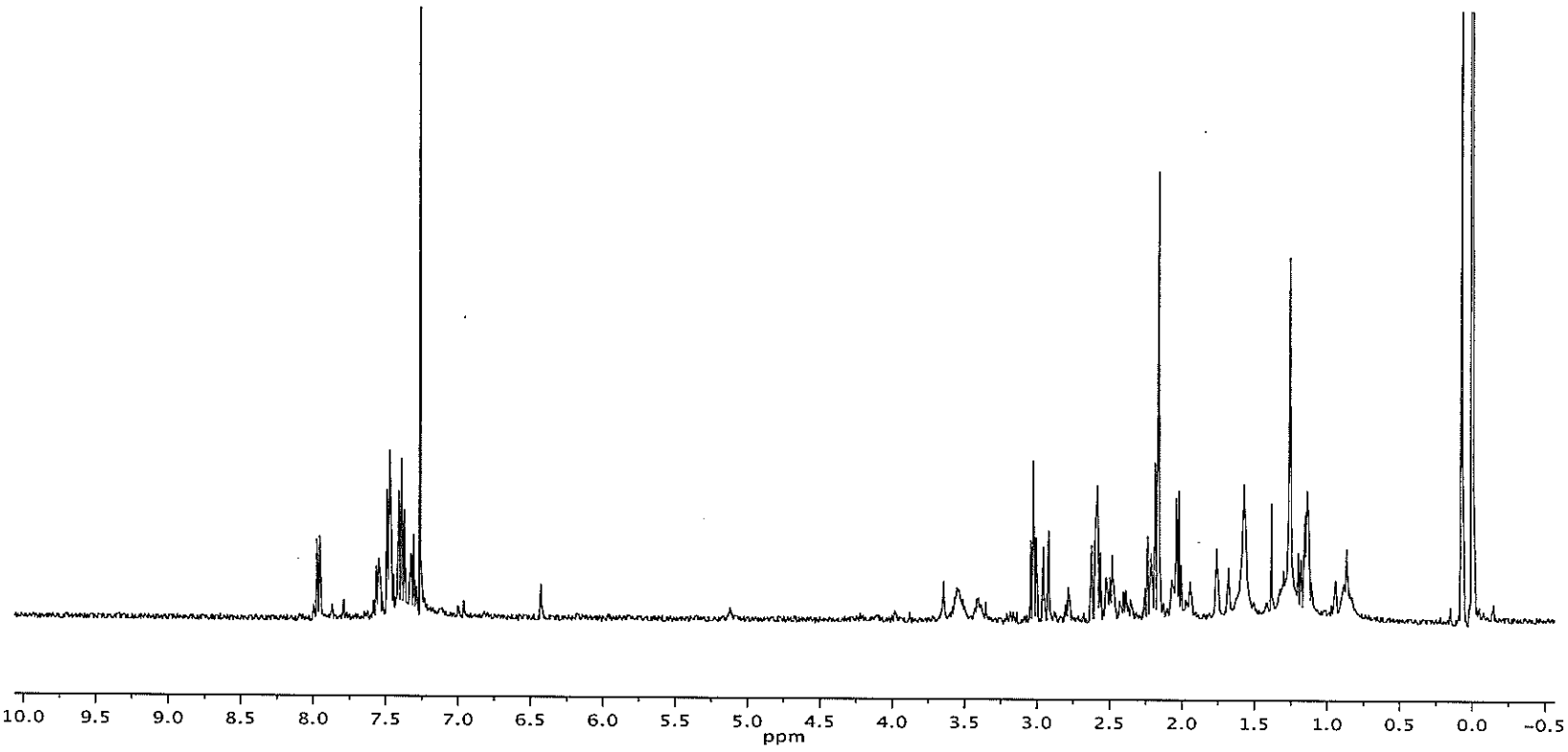

H3C
CH3
Si
CH3
CH3
O
CH3
O
+NBu4-F-
rt, 12 h
O
O
+
O
OH
+
O
O

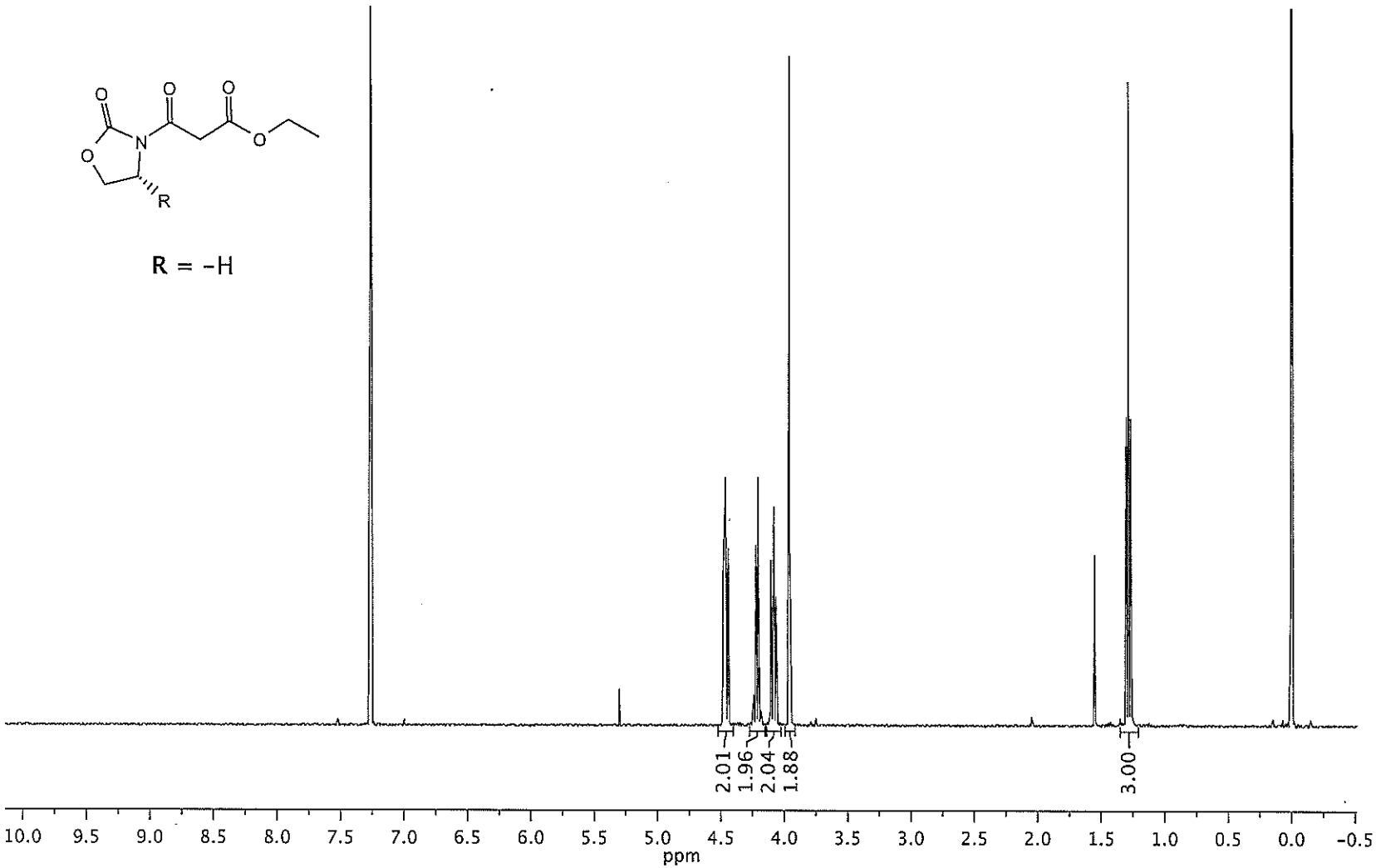
35 24 16 26

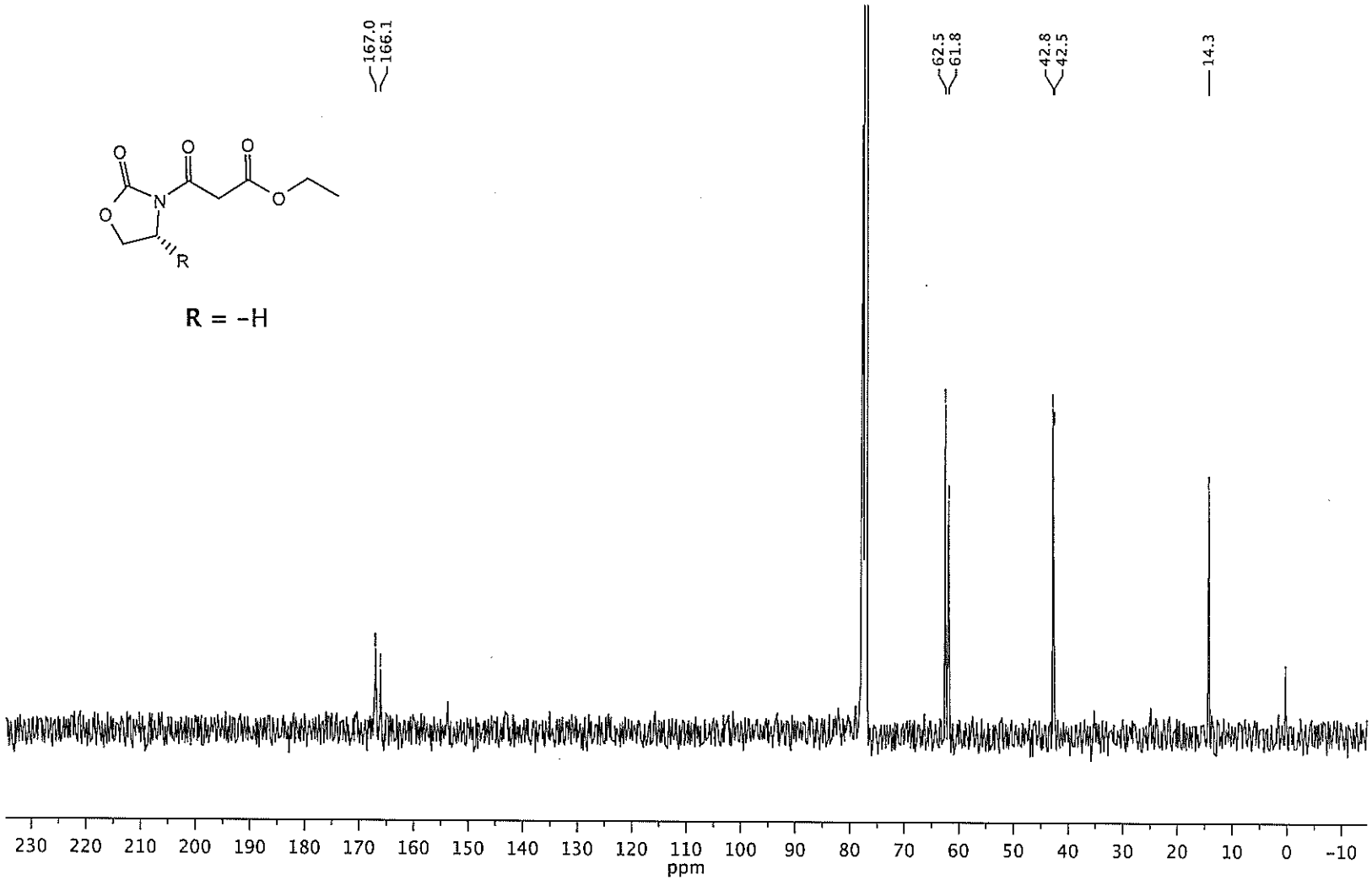

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

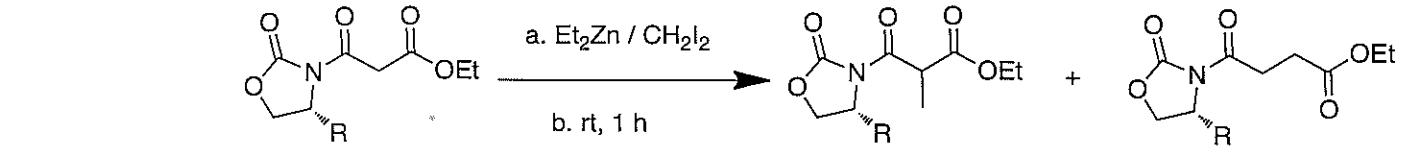

H3C
CH3
Si
CH3
O
CH3
O
+NBu4-F-
rt, 12 h
O
HO
O
O
O

35 28 27 26


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm


R = -H
2.01
1.96
2.04
1.88
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

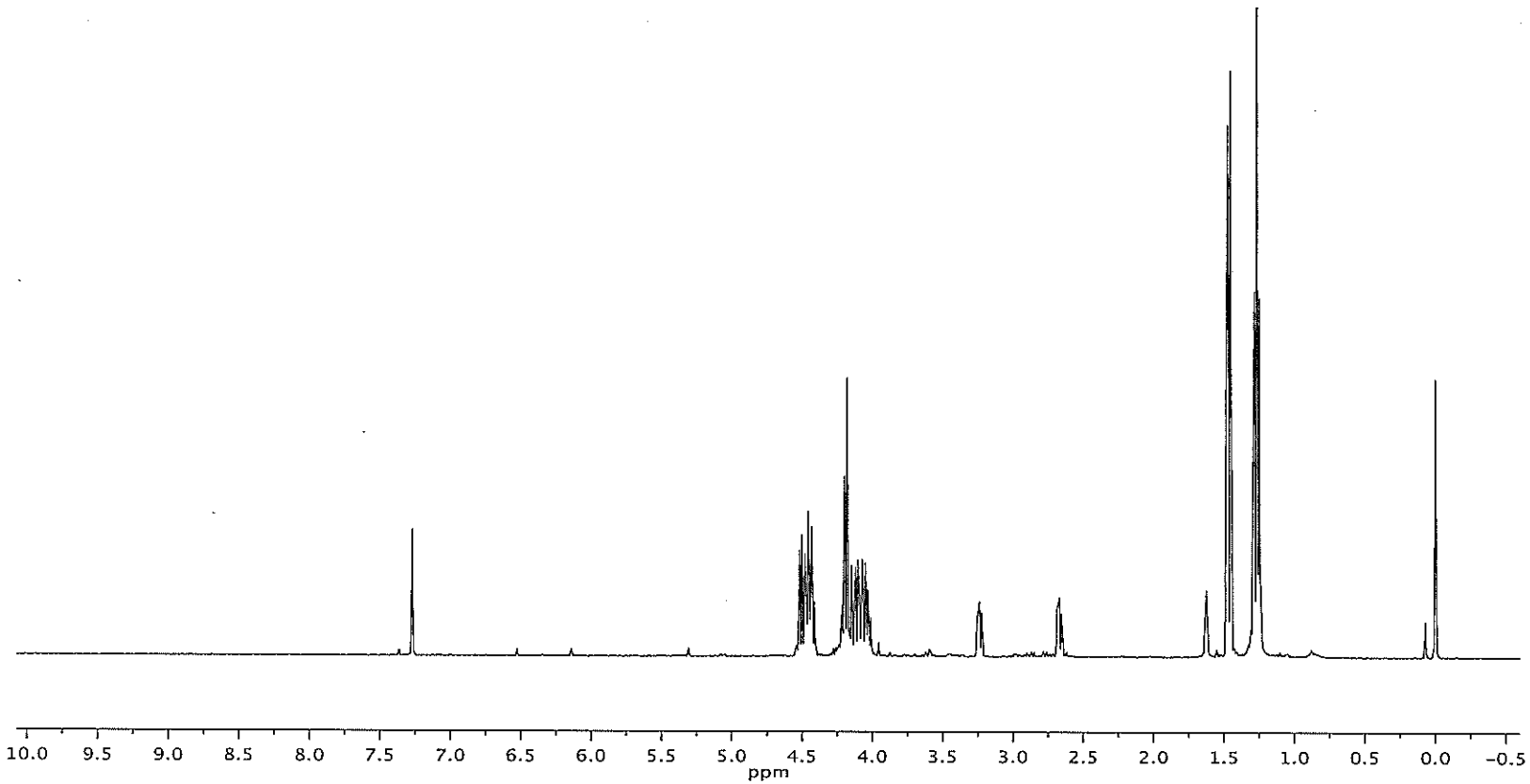

167.0
166.1
62.5
61.8
42.8
42.5
14.3
R
R = -H
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

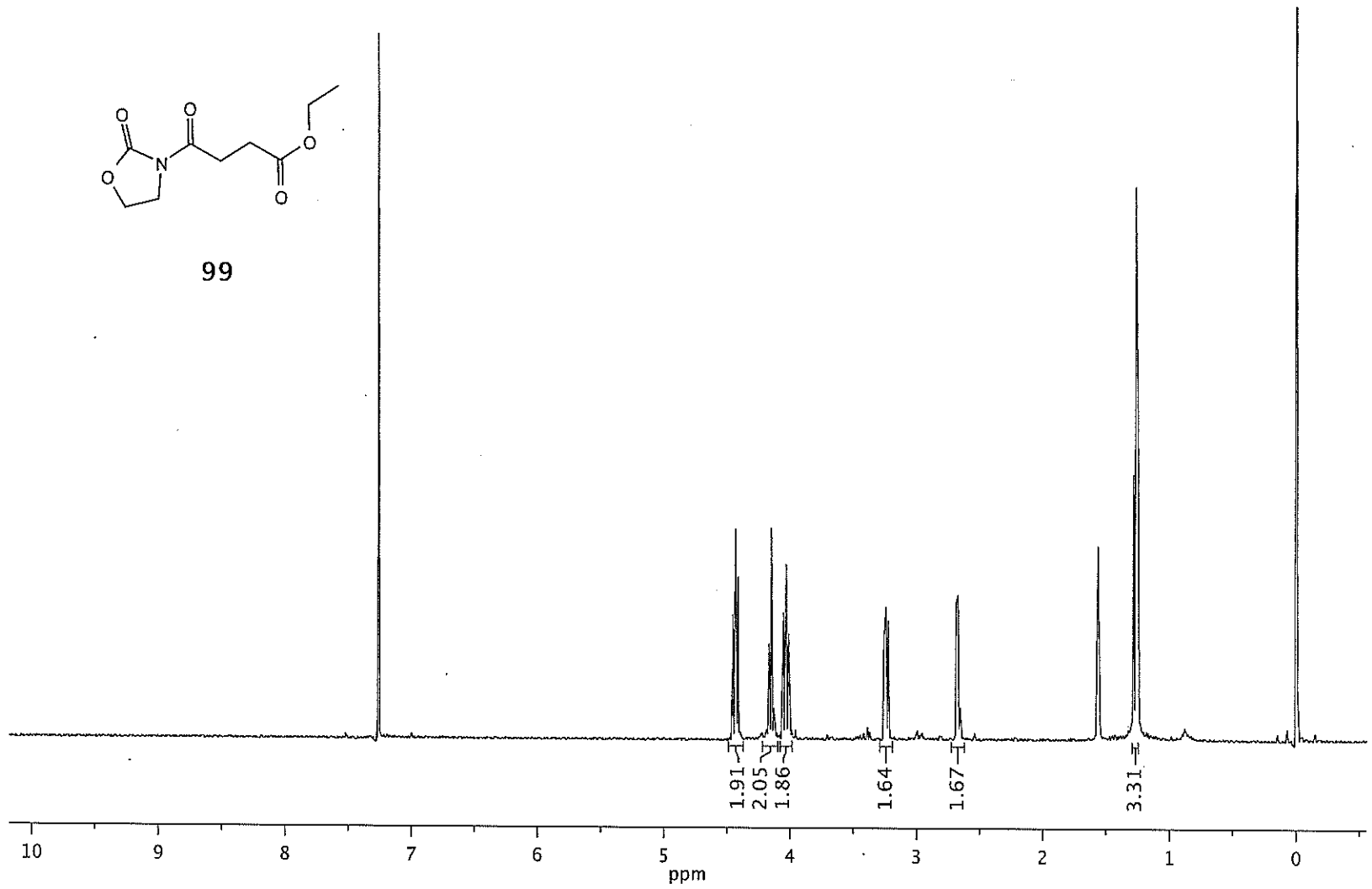

a. Et_2Zn / CH_2I_2
b. rt, 1 h
OEt
R
+
OEt
R
OEt
R

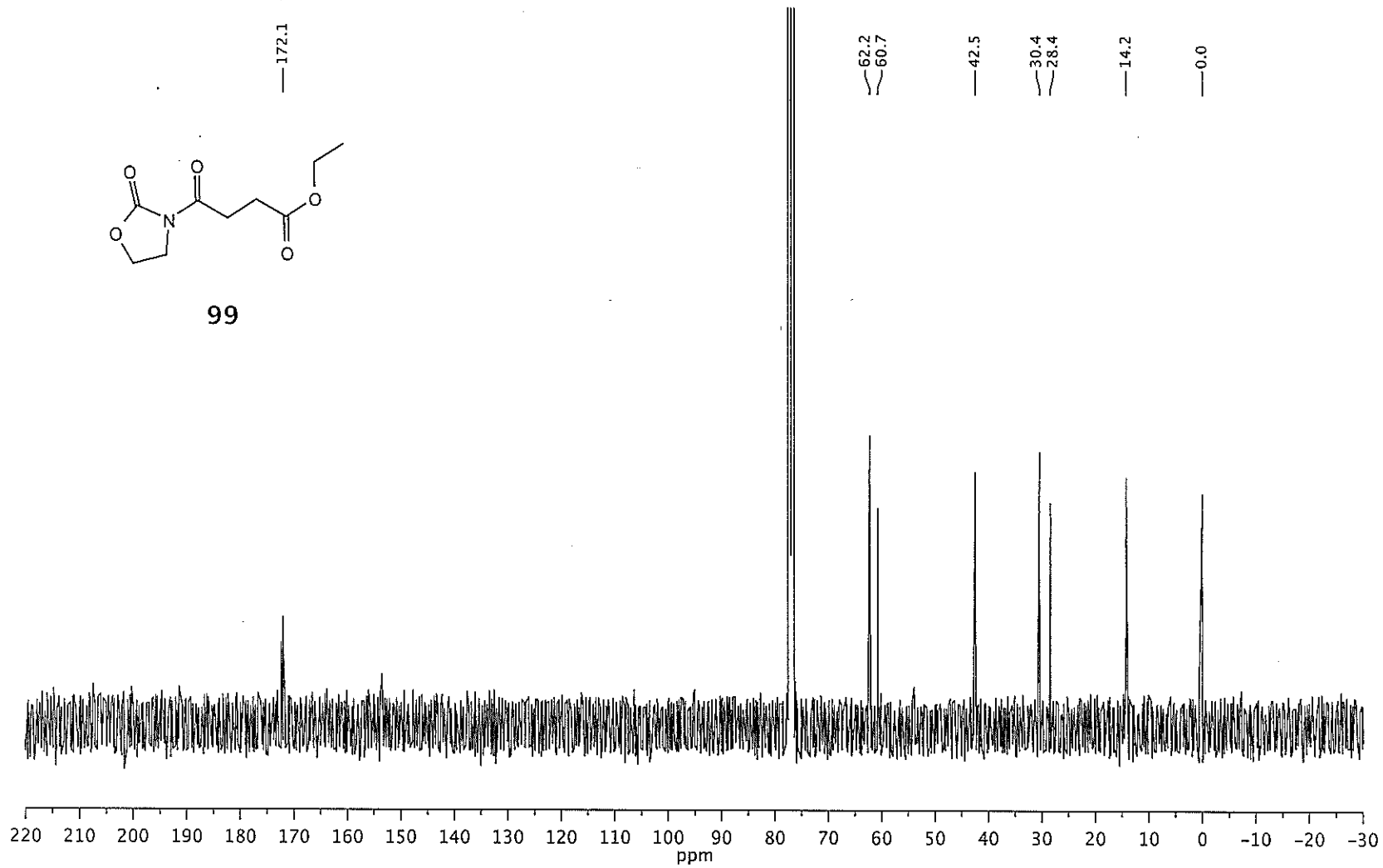
R = -H

98

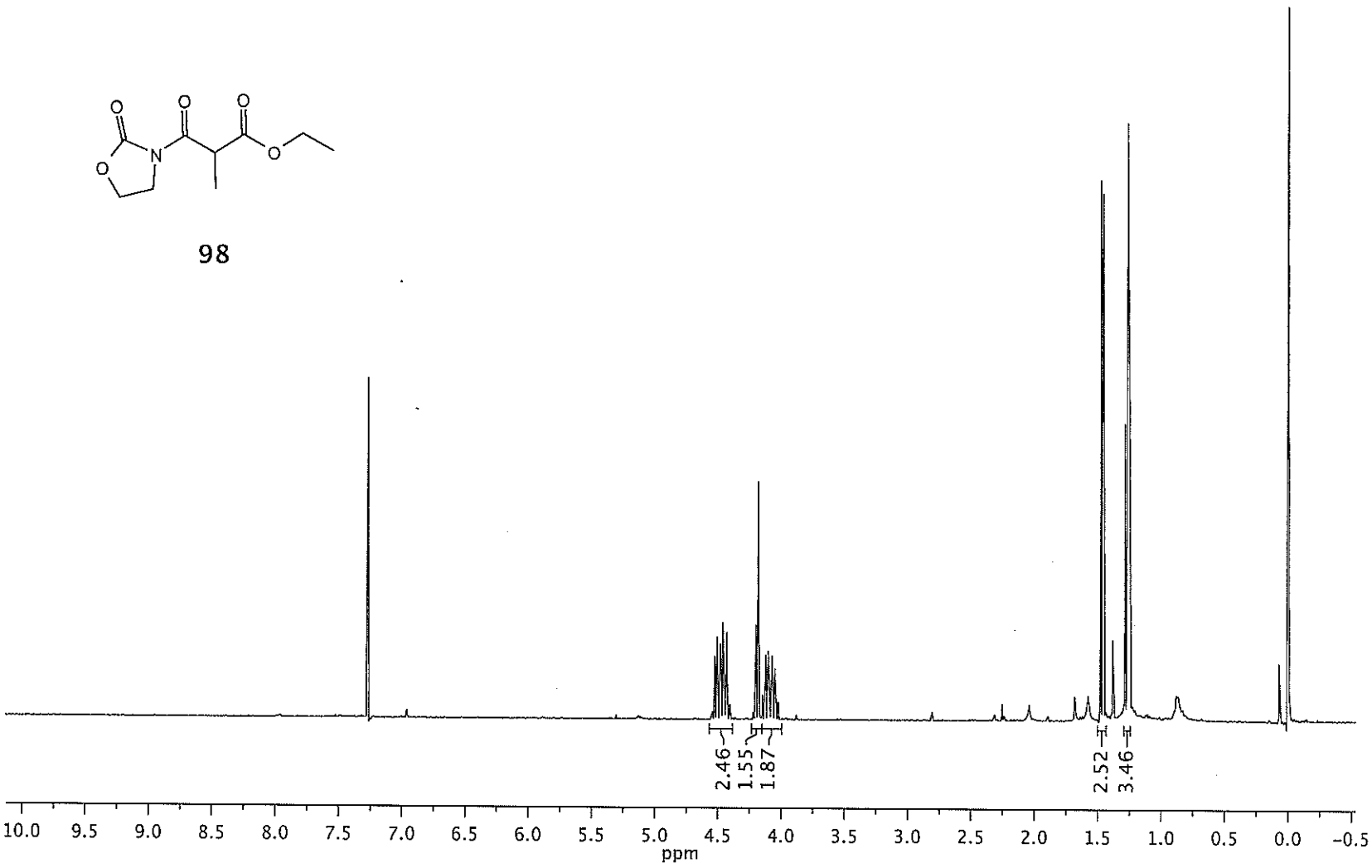
99

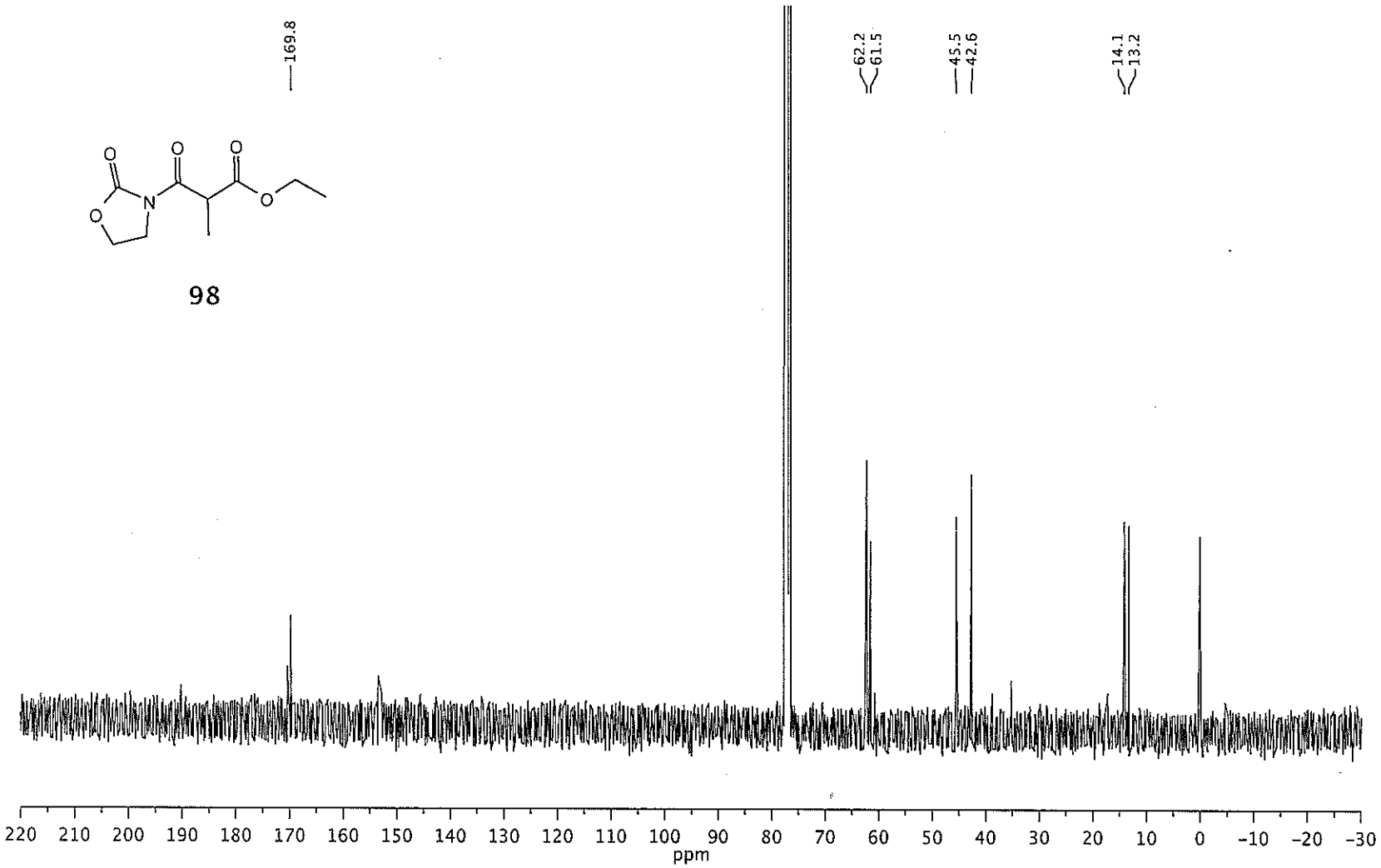

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm


99
1.91
2.05
1.86
1.64
1.67
3.31
10
9
8
7
6
5
4
3
2
1
0
ppm

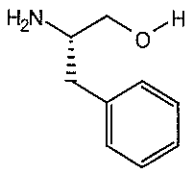

172.1
62.2
60.7
42.5
30.4
28.4
14.2
0.0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
ppm

99

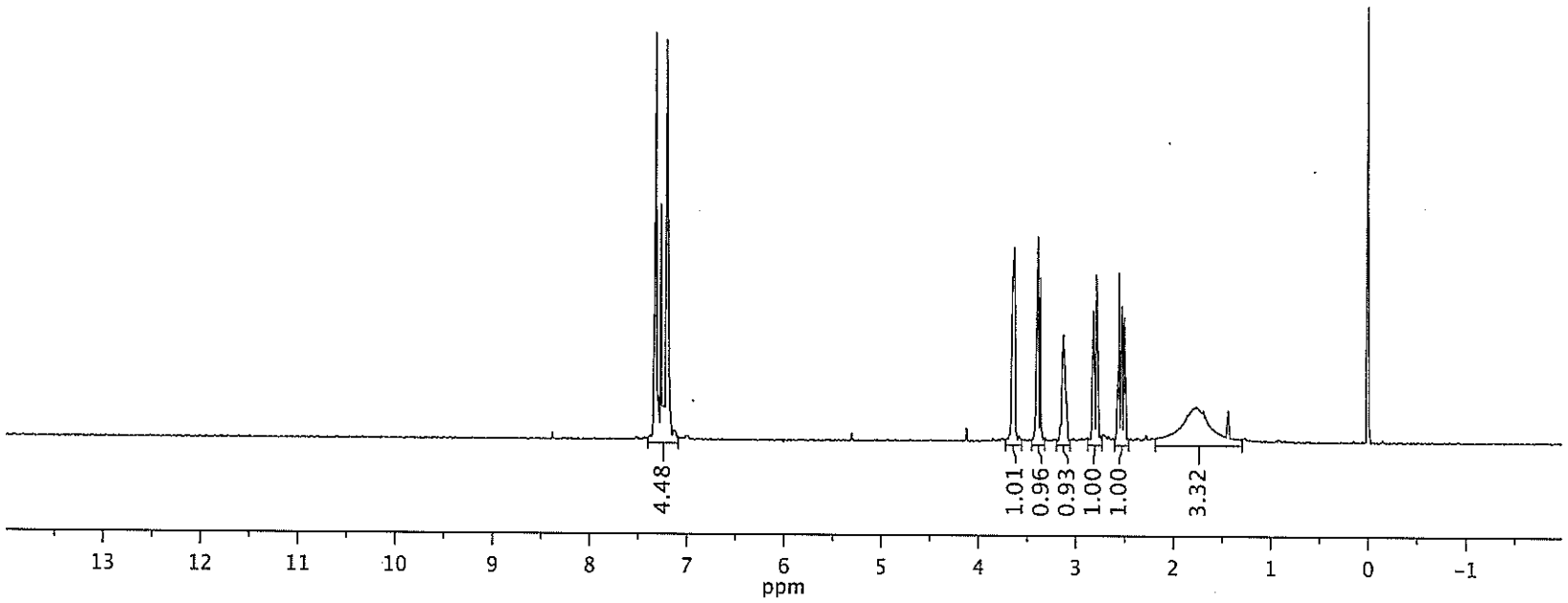

O
O
O
N
O
O
98
2.46
1.55
1.87
2.52
3.46
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

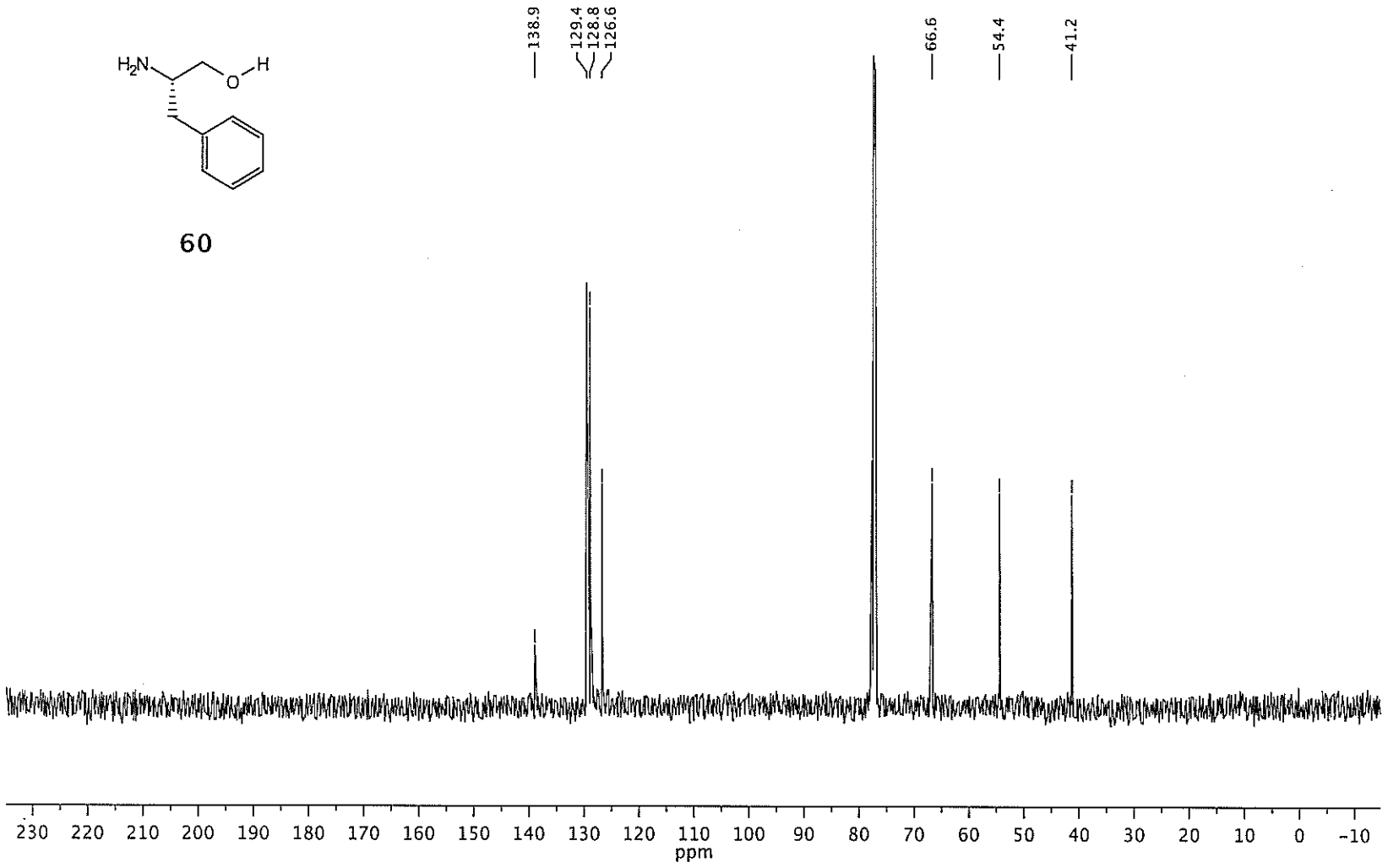

169.8
62.2
61.5
45.5
42.6
14.1
13.2
O
O
O
O
N
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
ppm

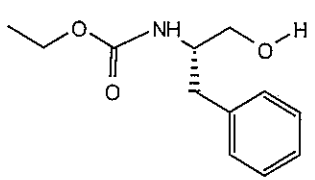
98



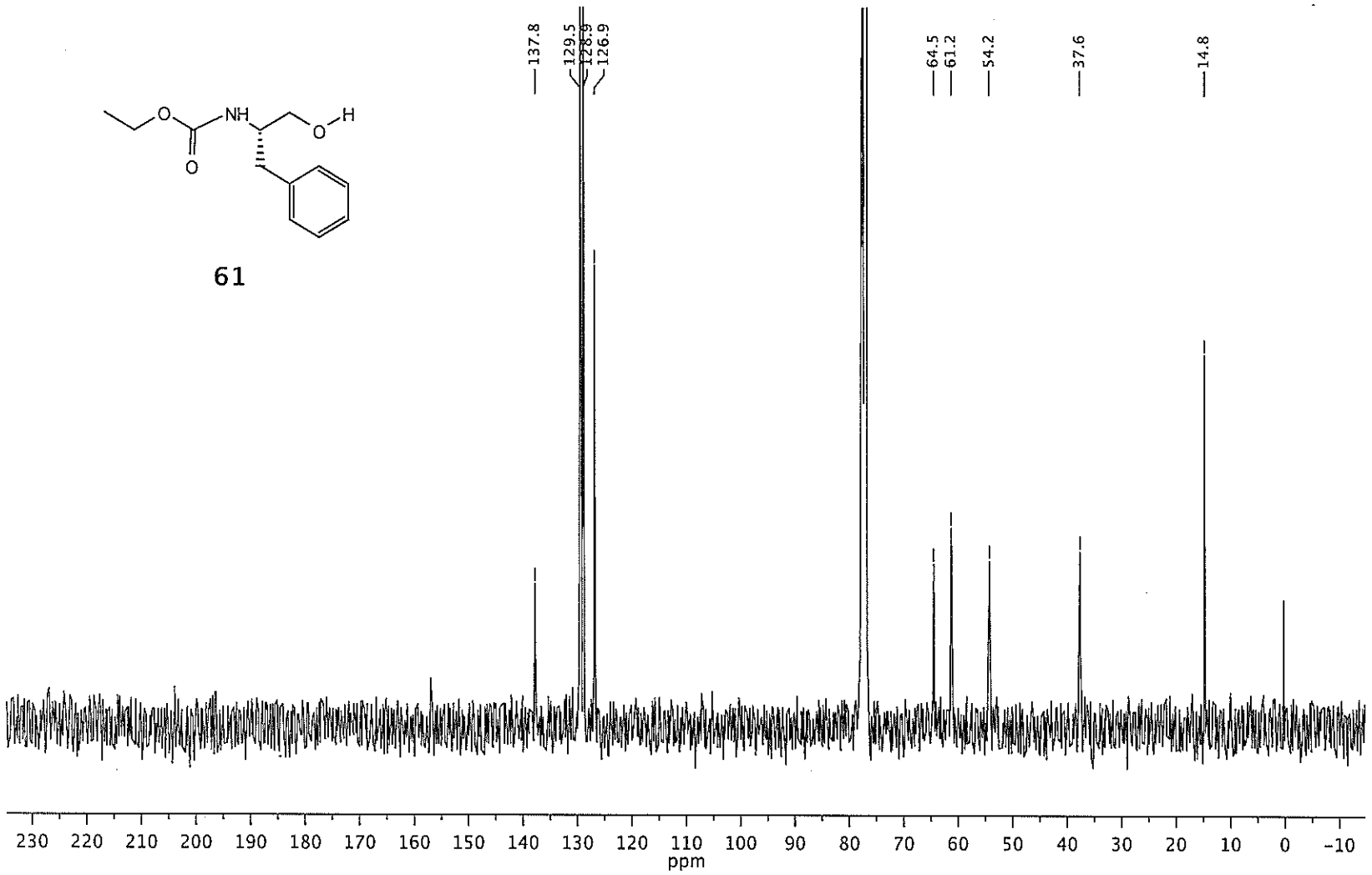
60

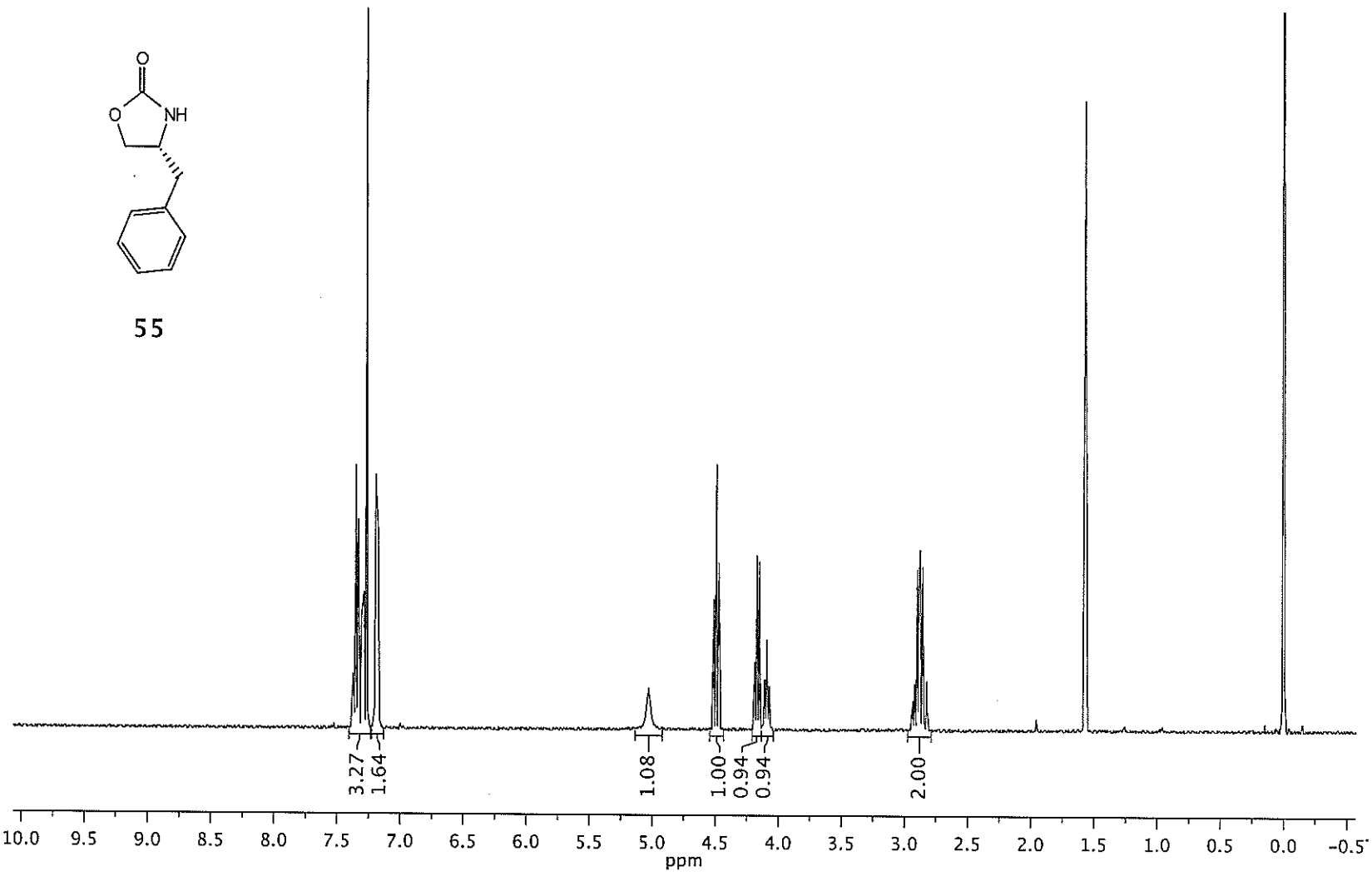


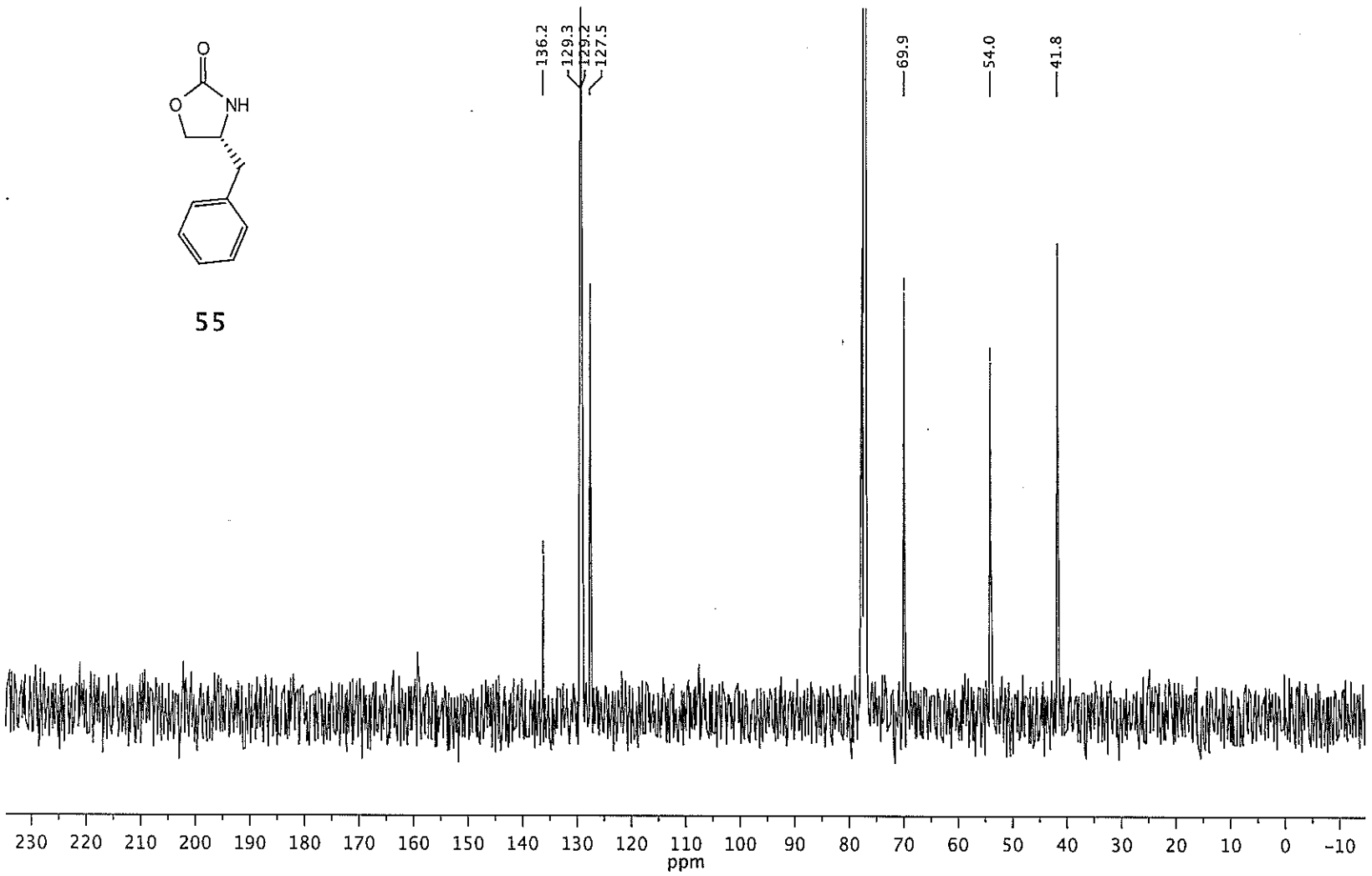

H2N
O
H
60
138.9
129.4
128.8
126.6
66.6
54.4
41.2
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

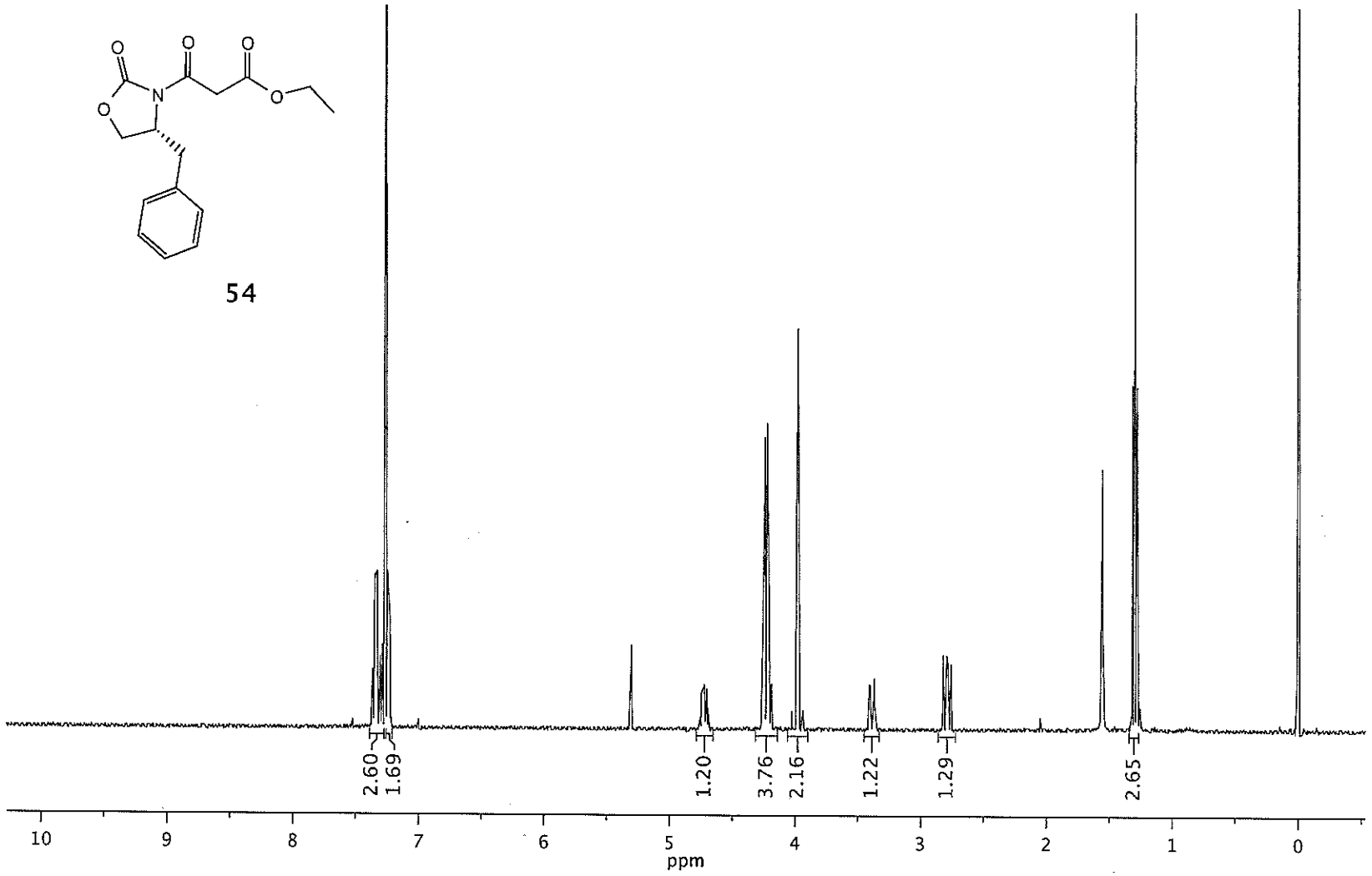


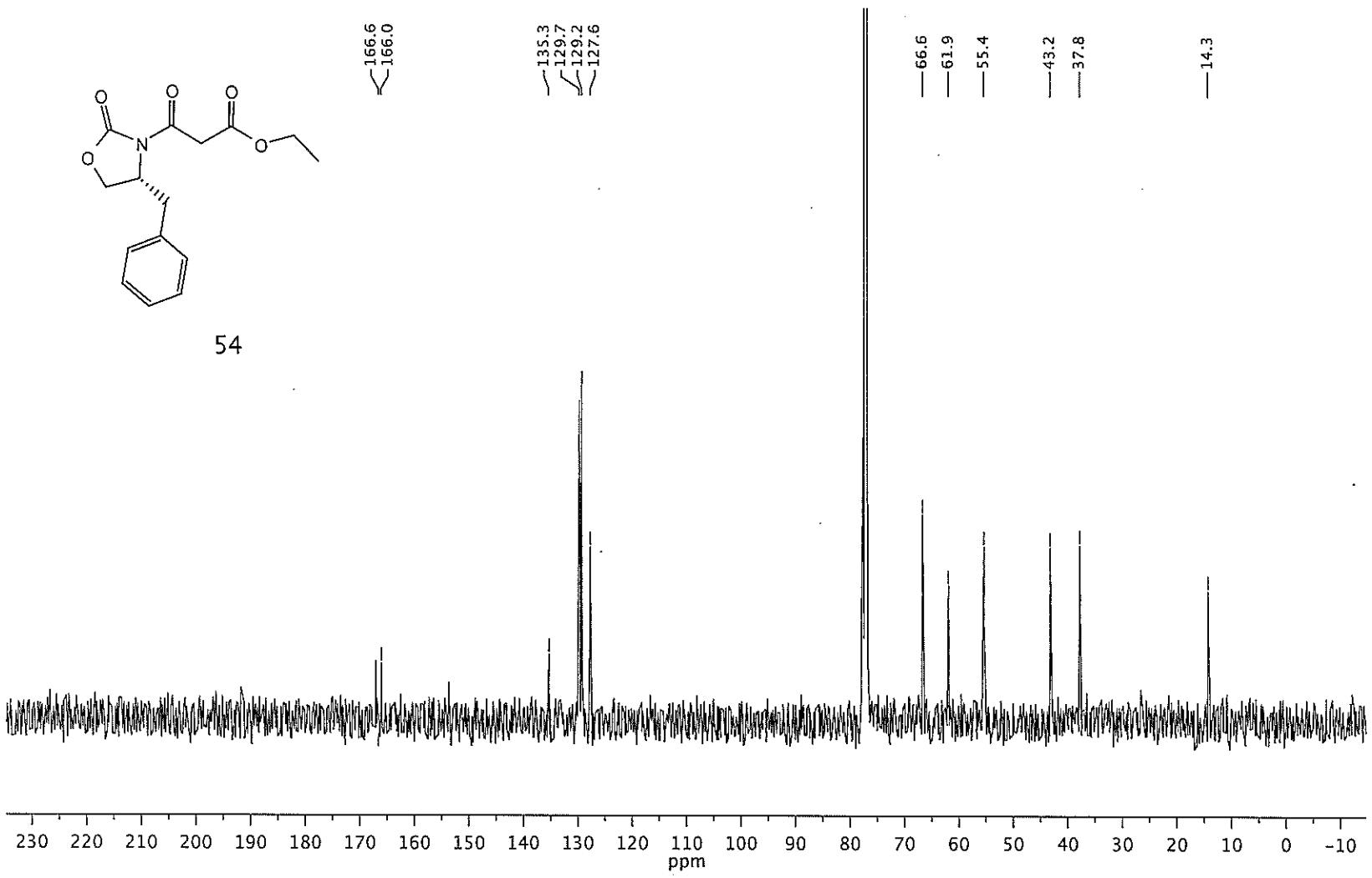
61


137.8
129.5
128.9
126.9
64.5
61.2
54.2
37.6
14.8
O
NH
O
O
H
61
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

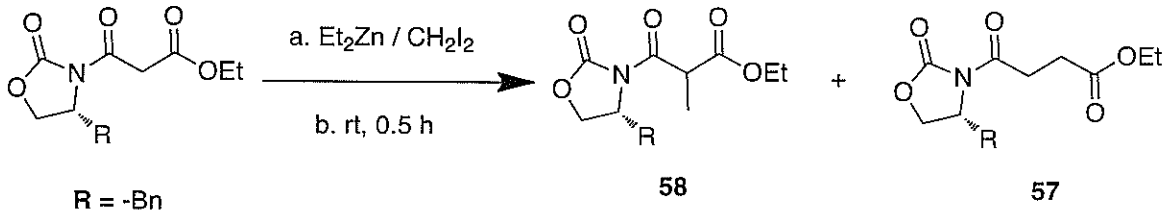

O
O
NH
55
3.27
1.64
1.08
1.00
0.94
0.94
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

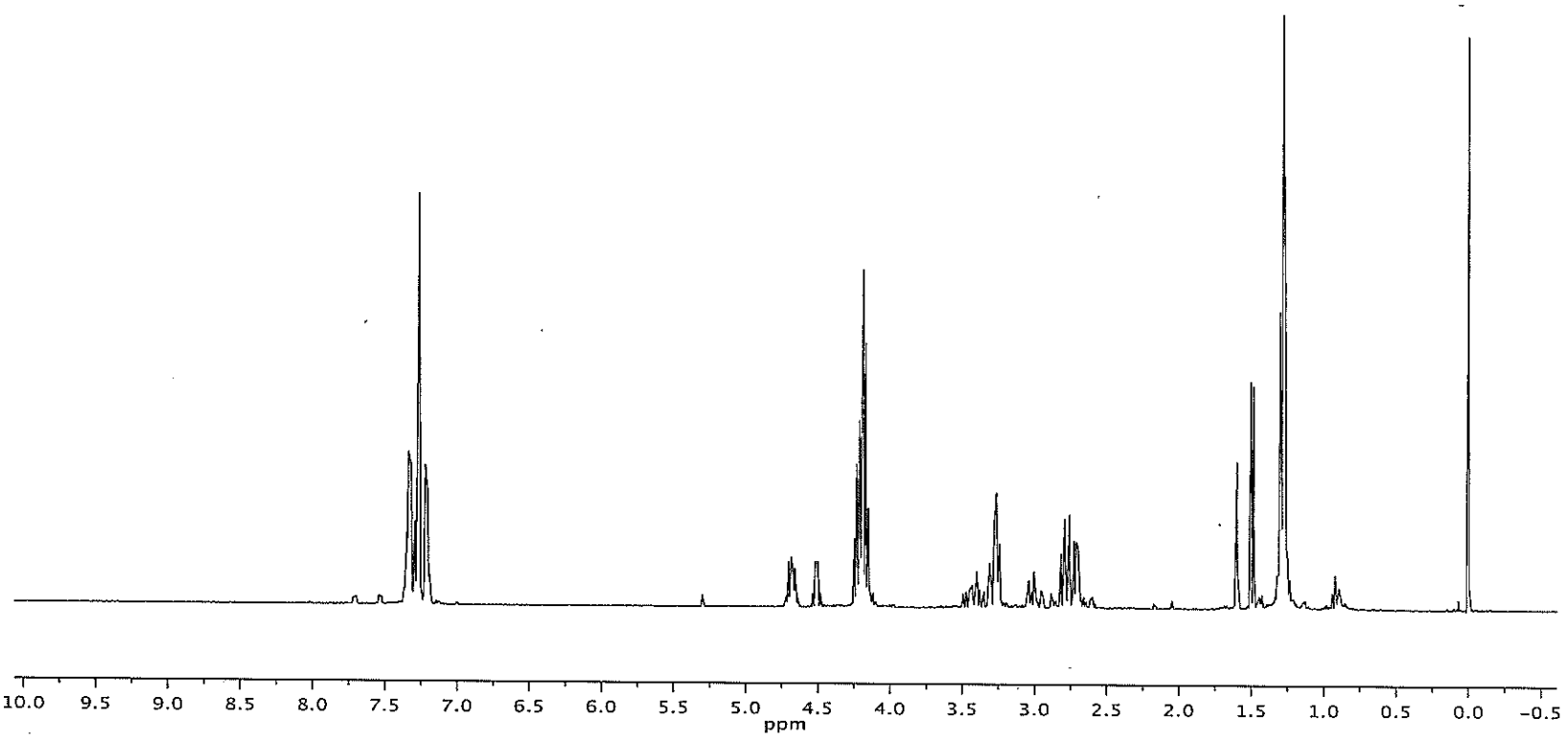

O
O
NH
55
136.2
129.3
129.2
127.5
69.9
54.0
41.8
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

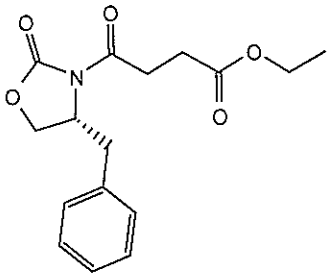

54
2.60
1.69
1.20
3.76
2.16
1.22
1.29
2.65
10
9
8
7
6
5
4
3
2
1
0
ppm


166.6
166.0
135.3
129.7
129.2
127.6
66.6
61.9
55.4
43.2
37.8
14.3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

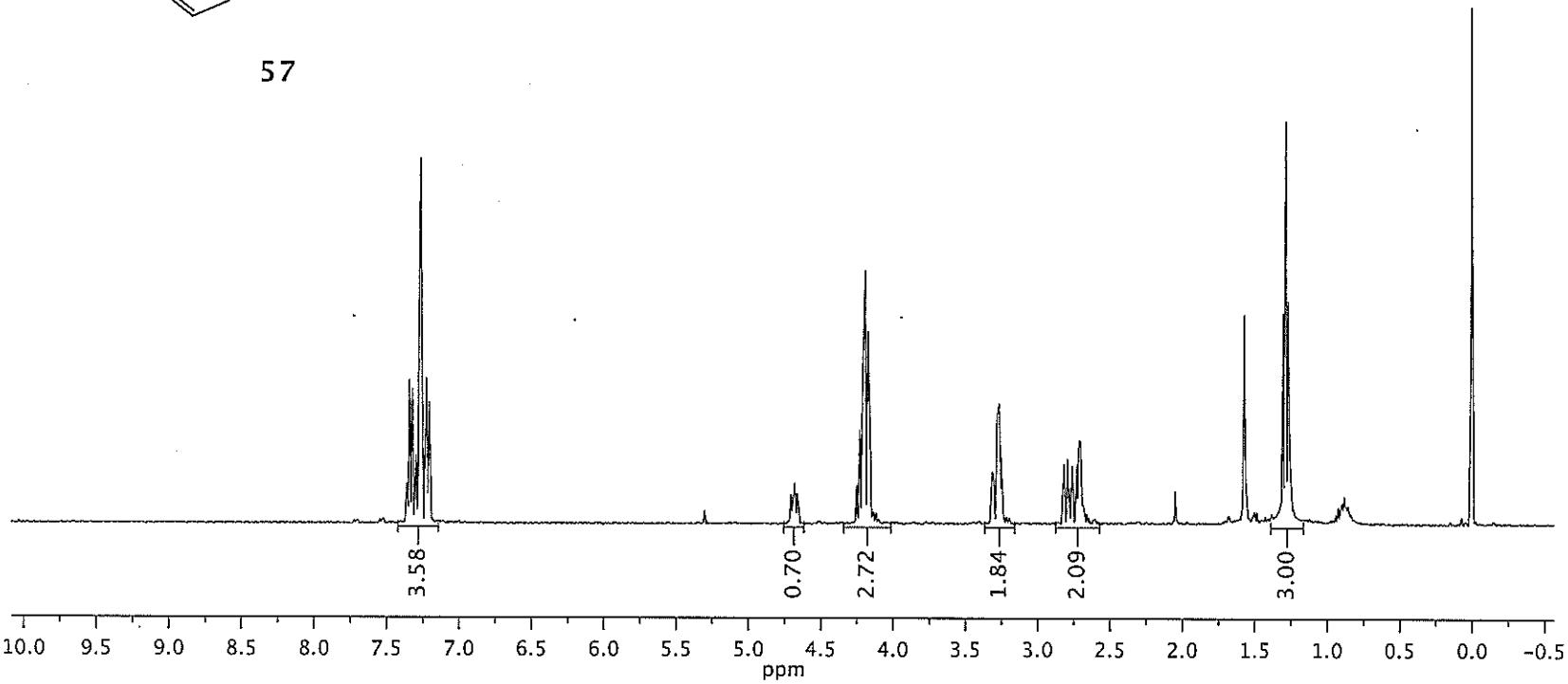
54

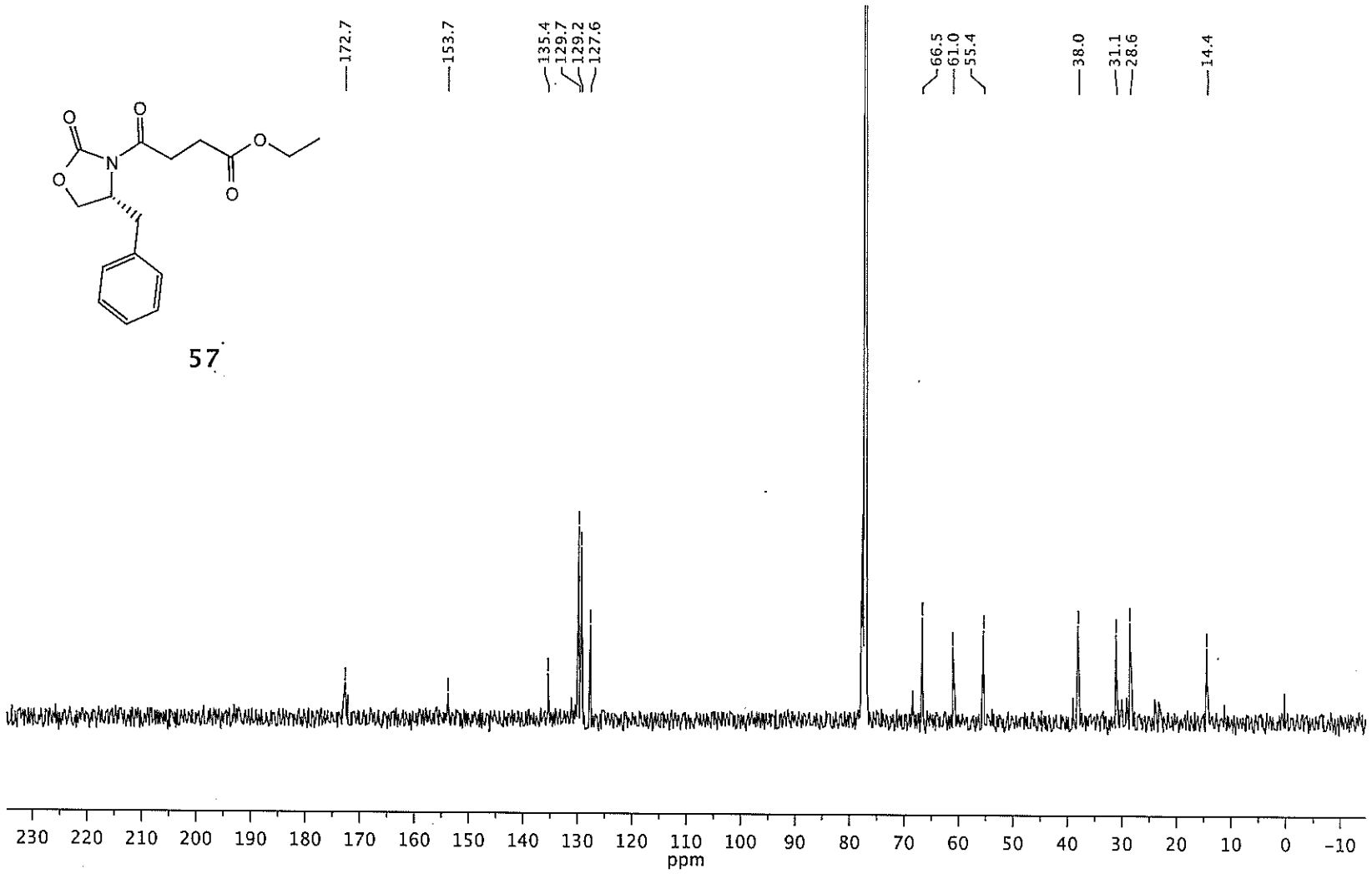

a. Et_2Zn / CH_2I_2
b. rt, 0.5 h
OEt
R
R = -Bn
58
57


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

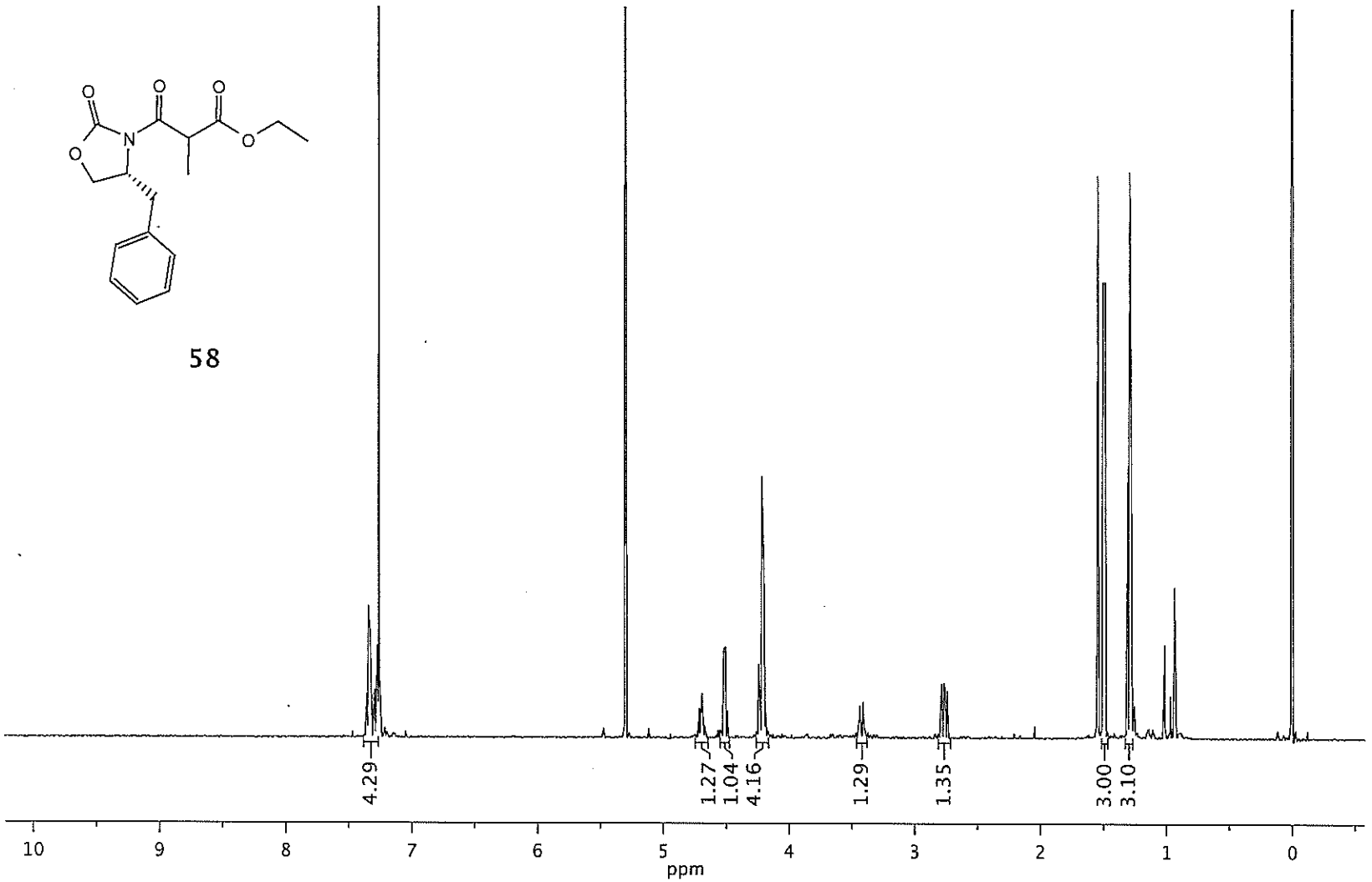


57

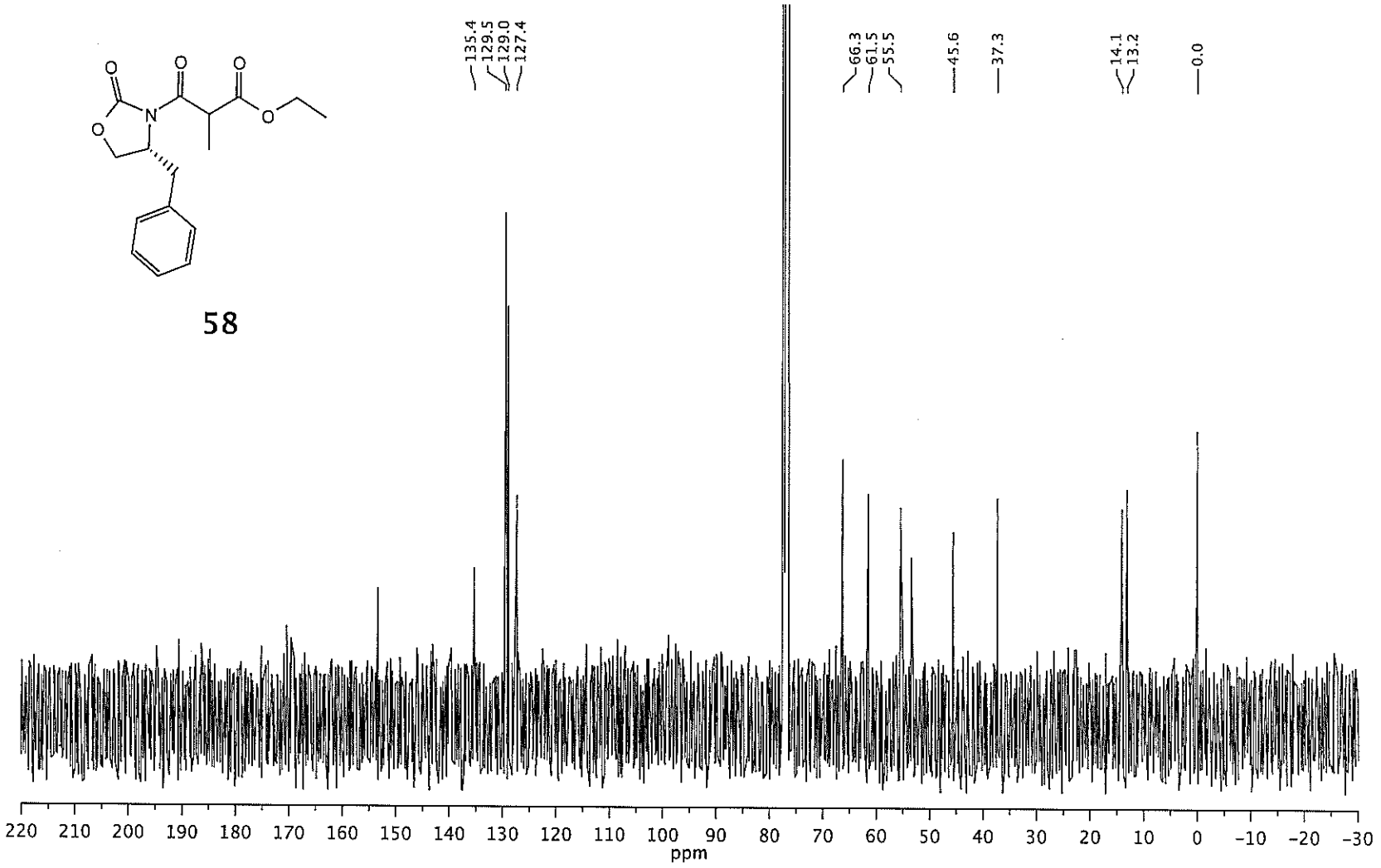

3.58
0.70
2.72
1.84
2.09
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm


172.7
153.7
135.4
129.7
129.2
127.6
66.5
61.0
55.4
38.0
31.1
28.6
14.4
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

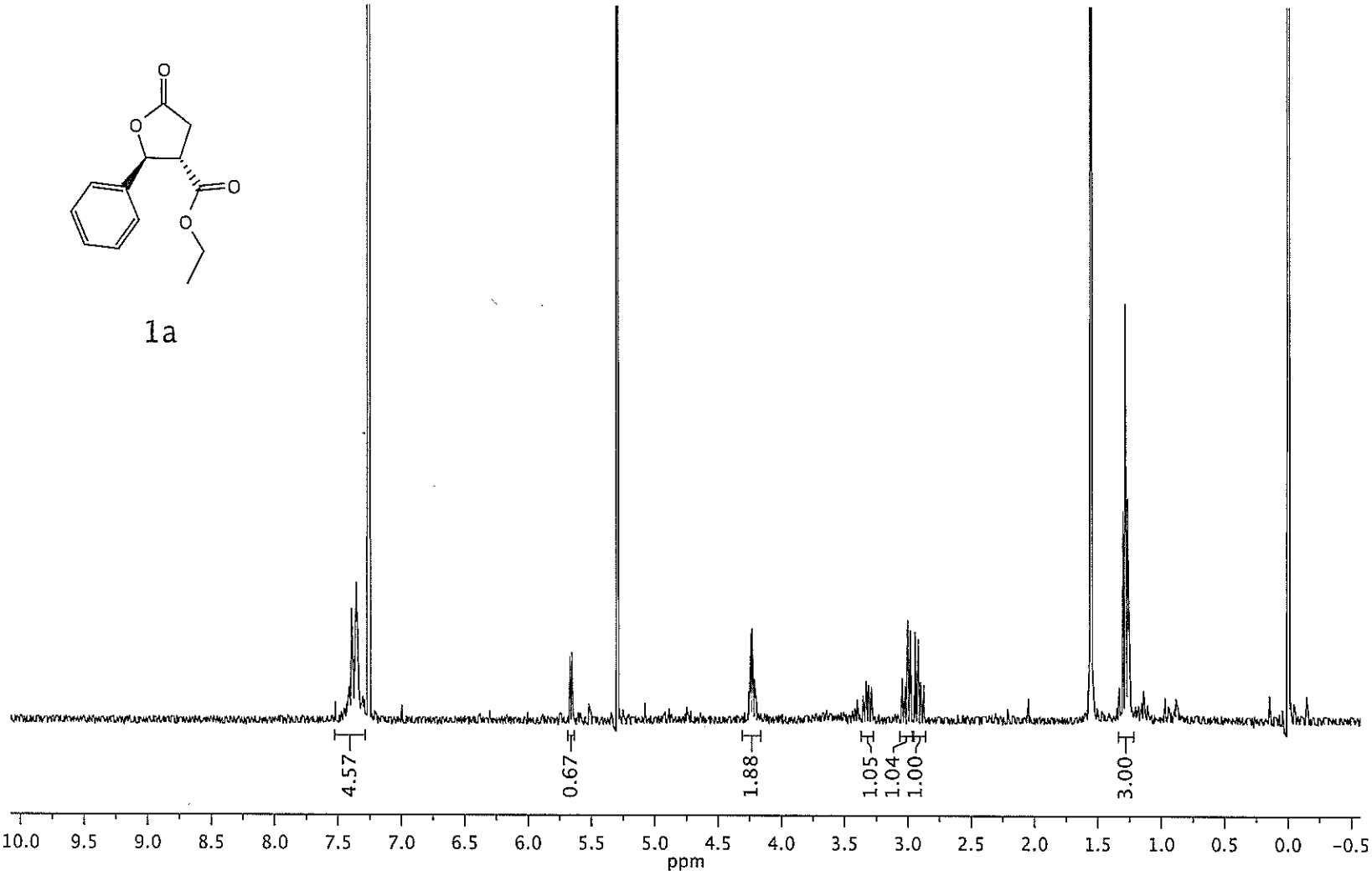
57

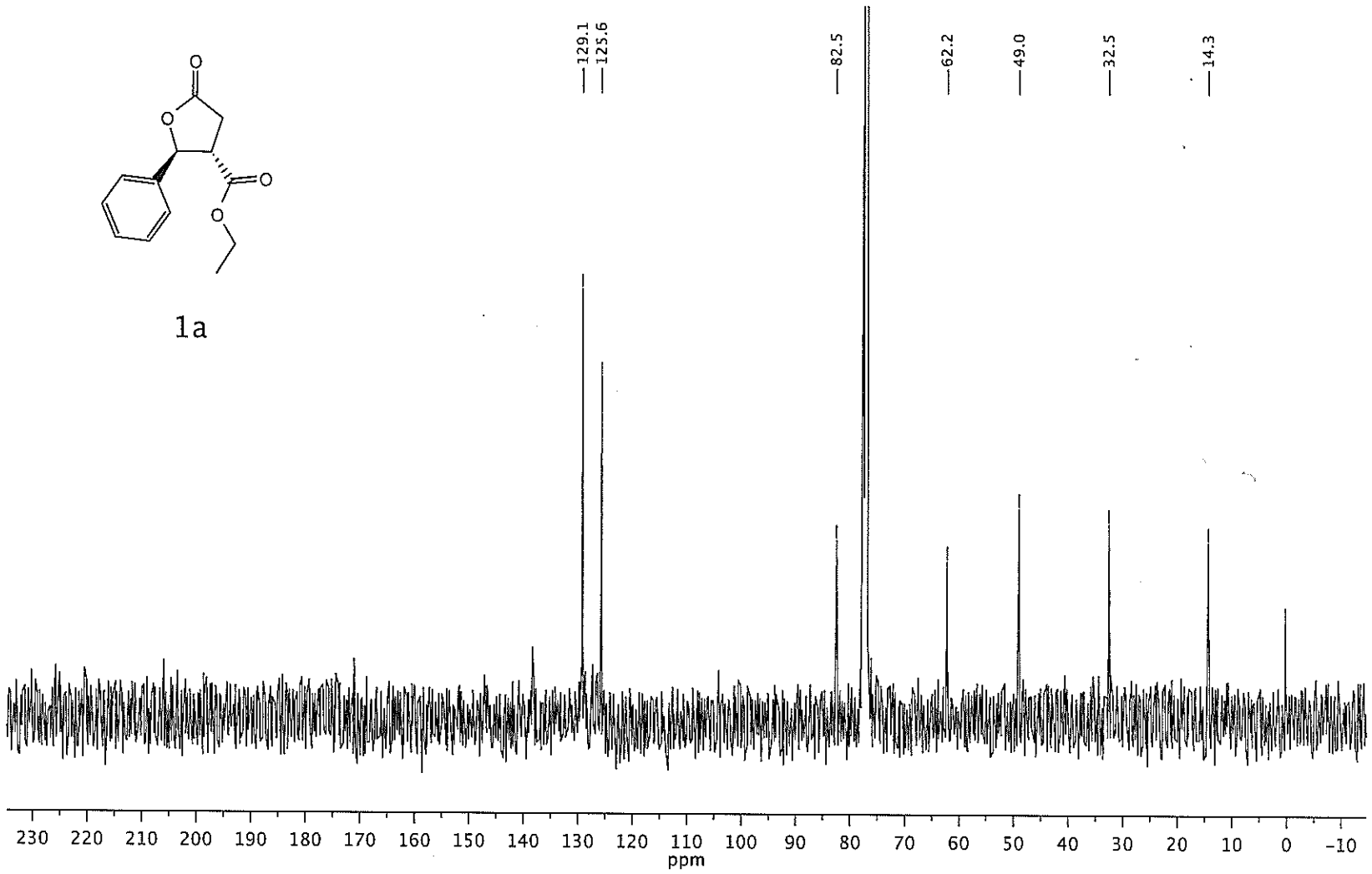


58

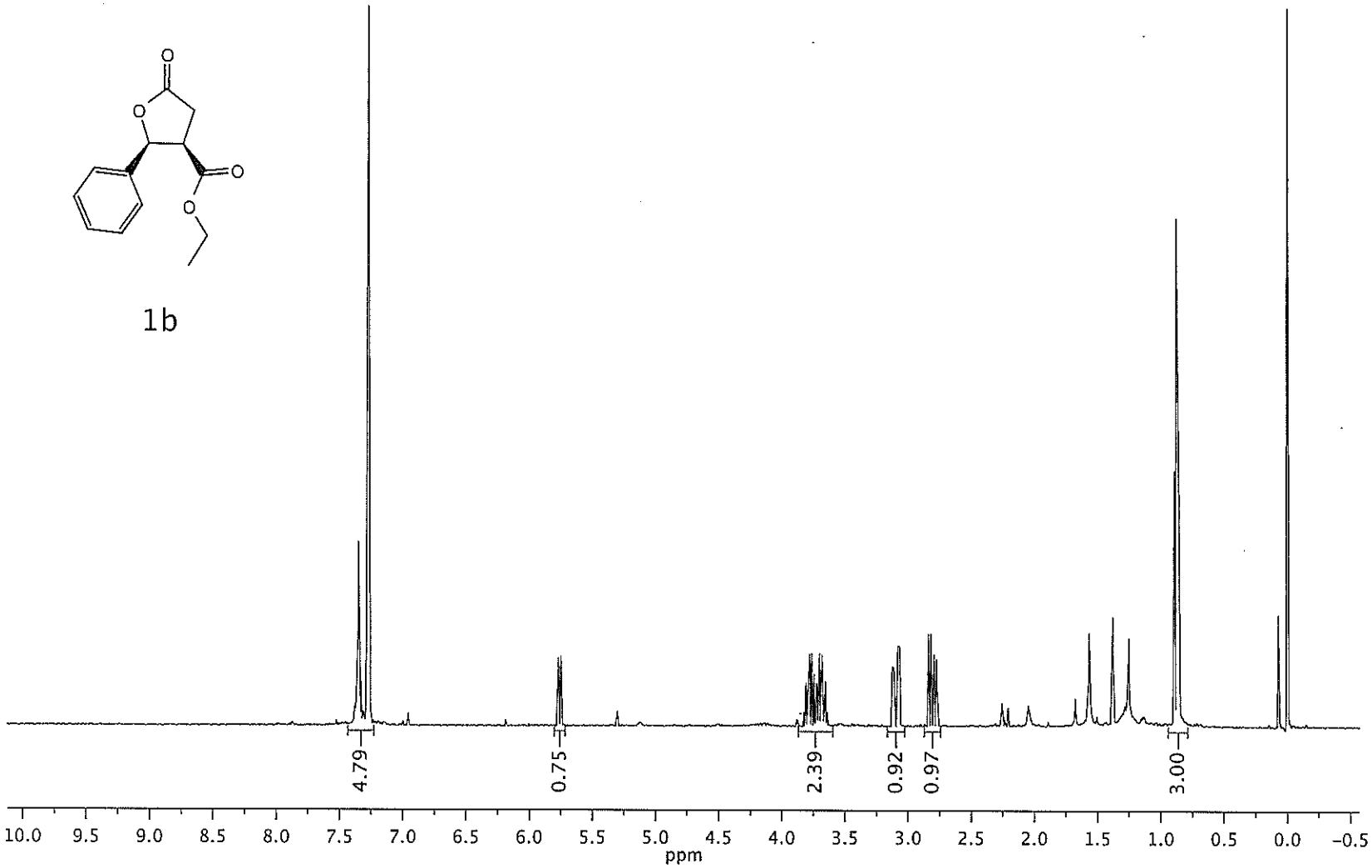

135.4
129.5
129.0
127.4
66.3
61.5
55.5
45.6
37.3
14.1
13.2
0.0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
ppm

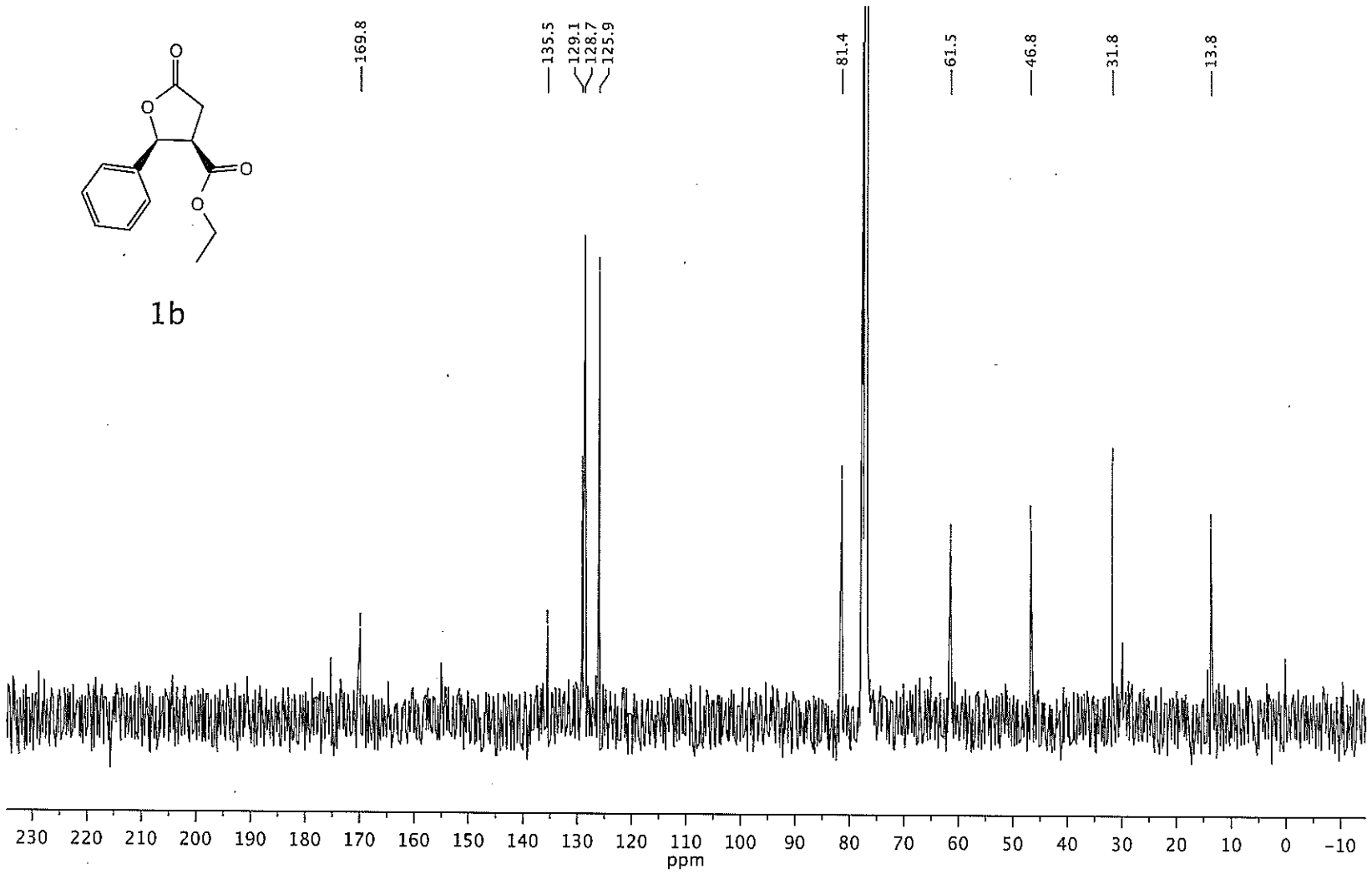
58

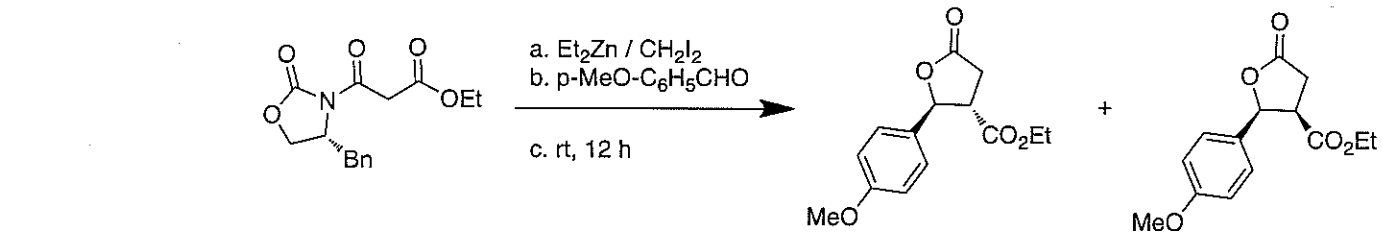

1a
4.57
0.67
1.88
1.05
1.04
1.00
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm


129.1
125.6
82.5
62.2
49.0
32.5
14.3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

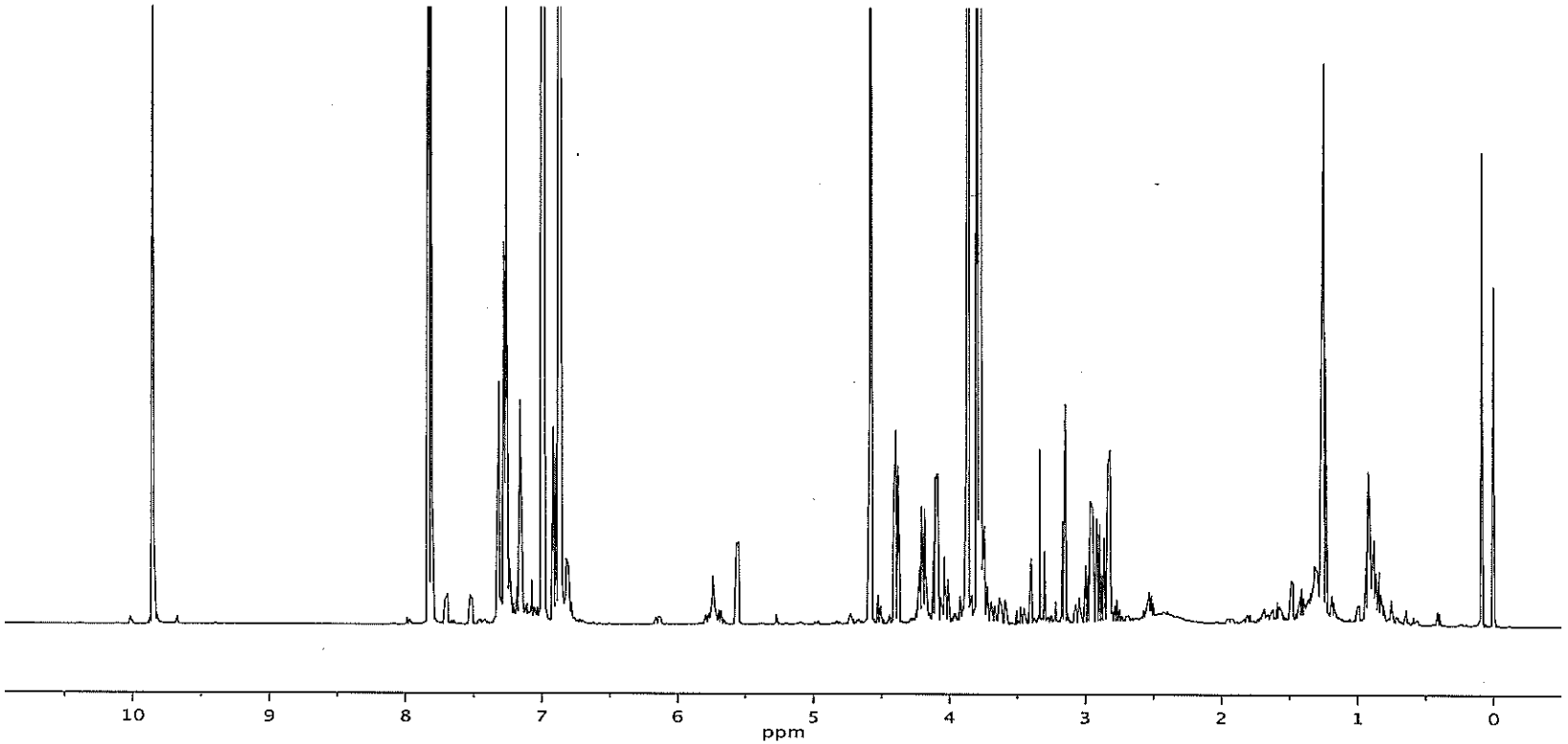
1a

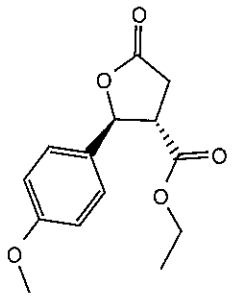

1b
4.79
0.75
2.39
0.92
0.97
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm


169.8
135.5
129.1
128.7
125.9
81.4
61.5
46.8
31.8
13.8
1b
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

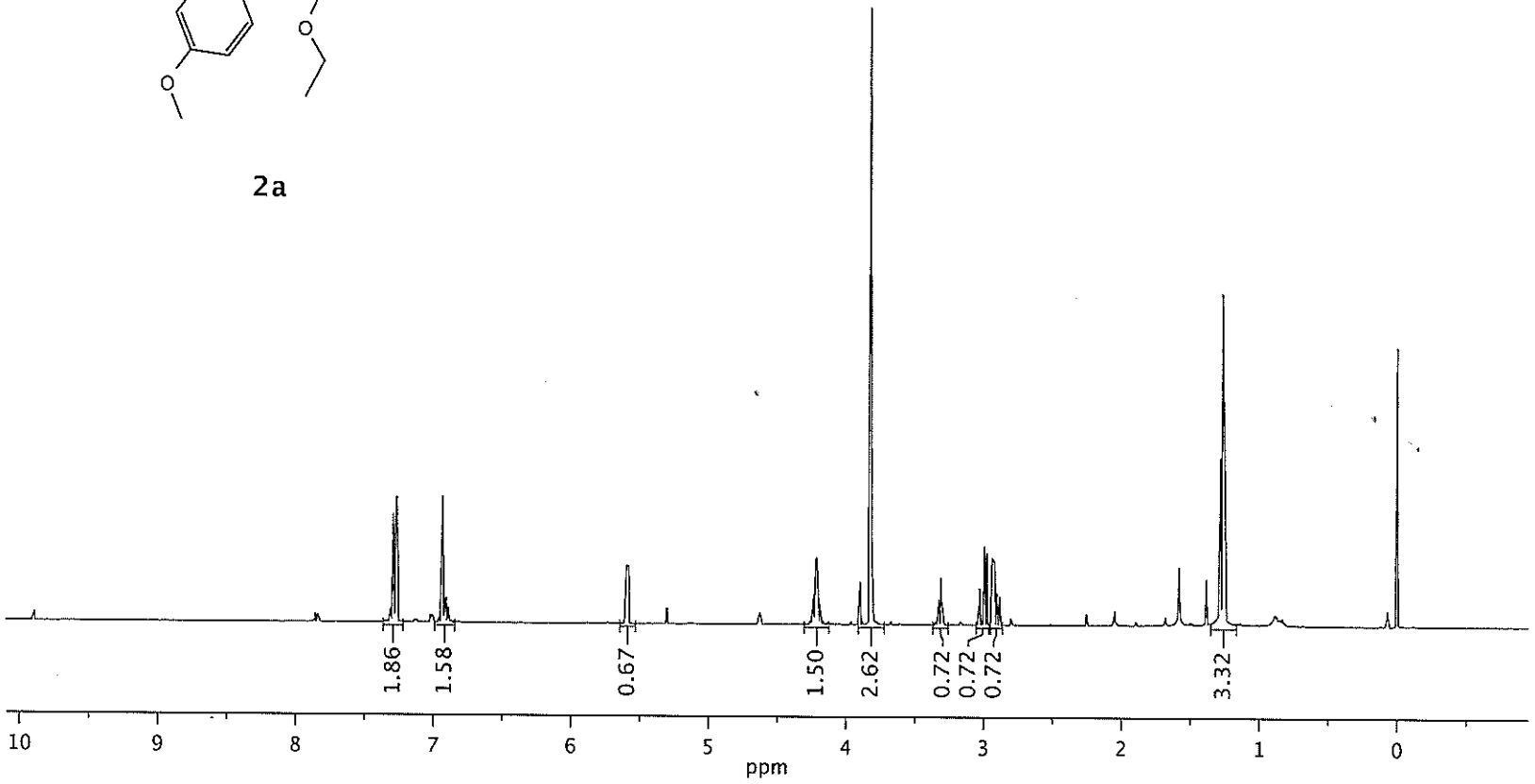

a. Et_2Zn / CH_2I_2
b. p-MeO-C_6H_5CHO
c. rt, 12 h
OEt
Bn
MeO
CO_2Et
+

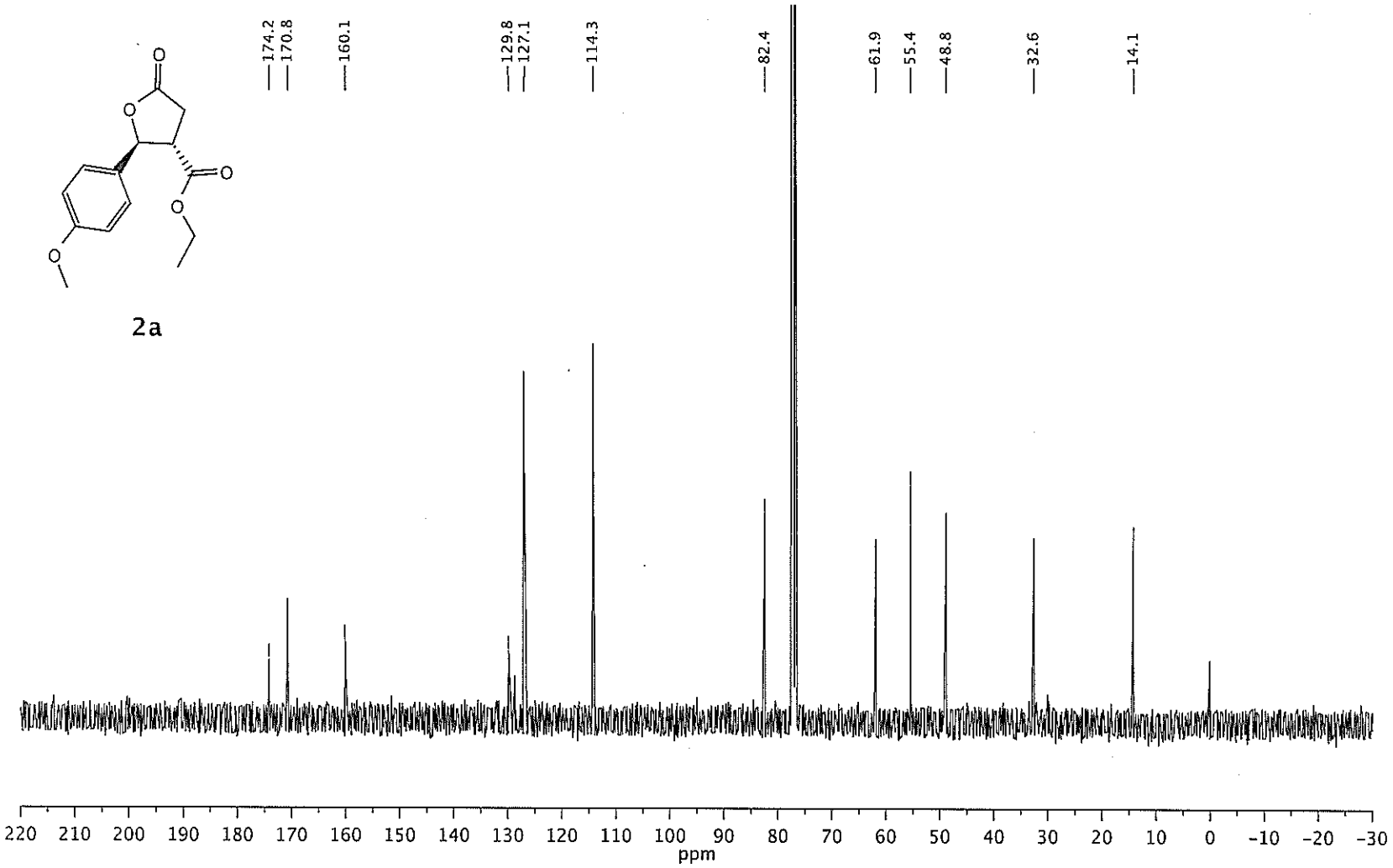
54 **2a** **2b**


10
9
8
7
6
5
4
3
2
1
0
ppm

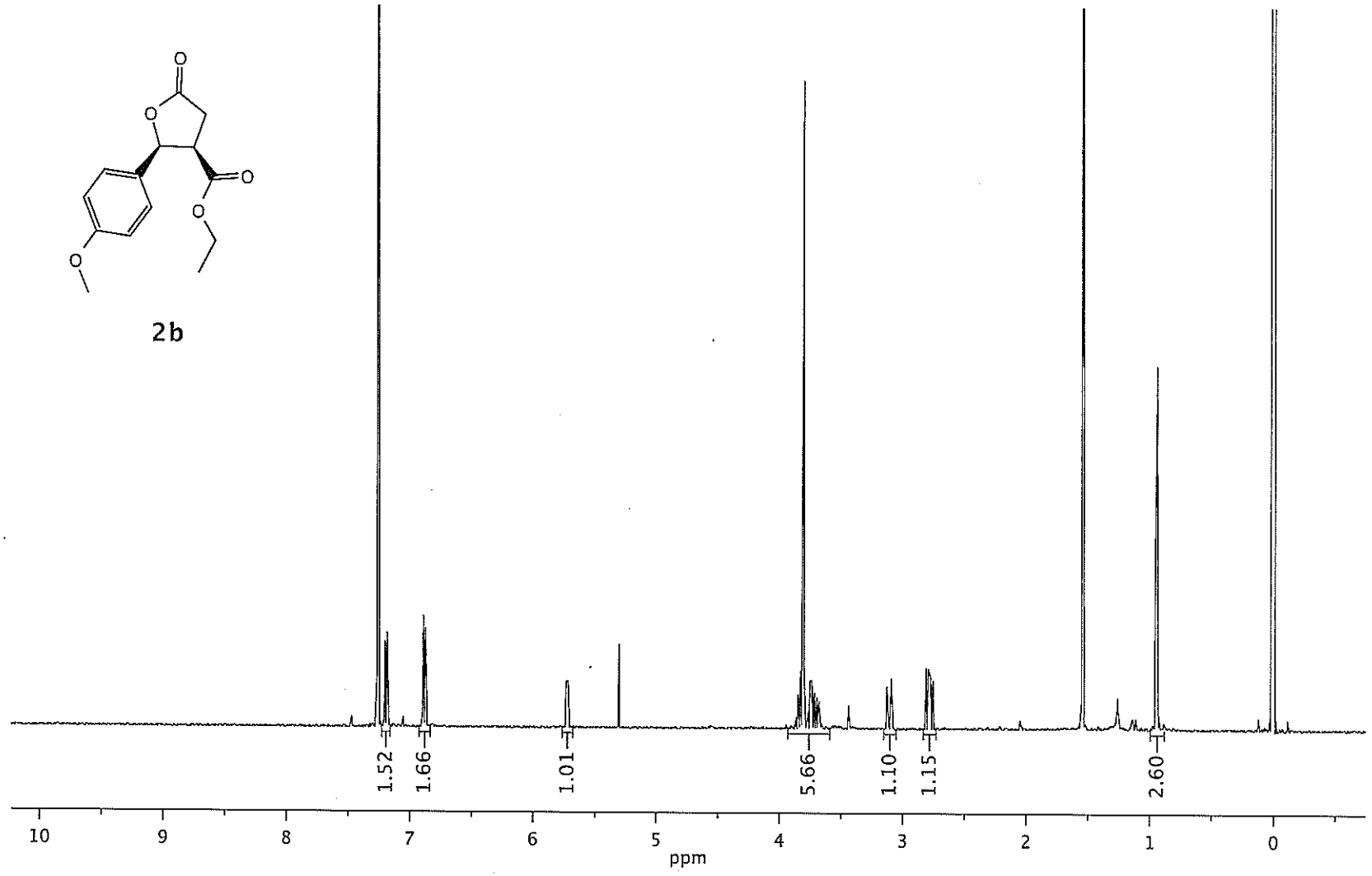


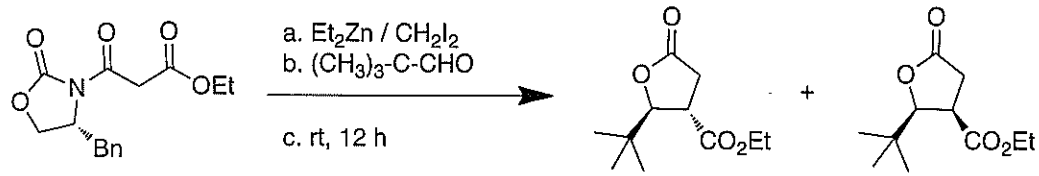
2a



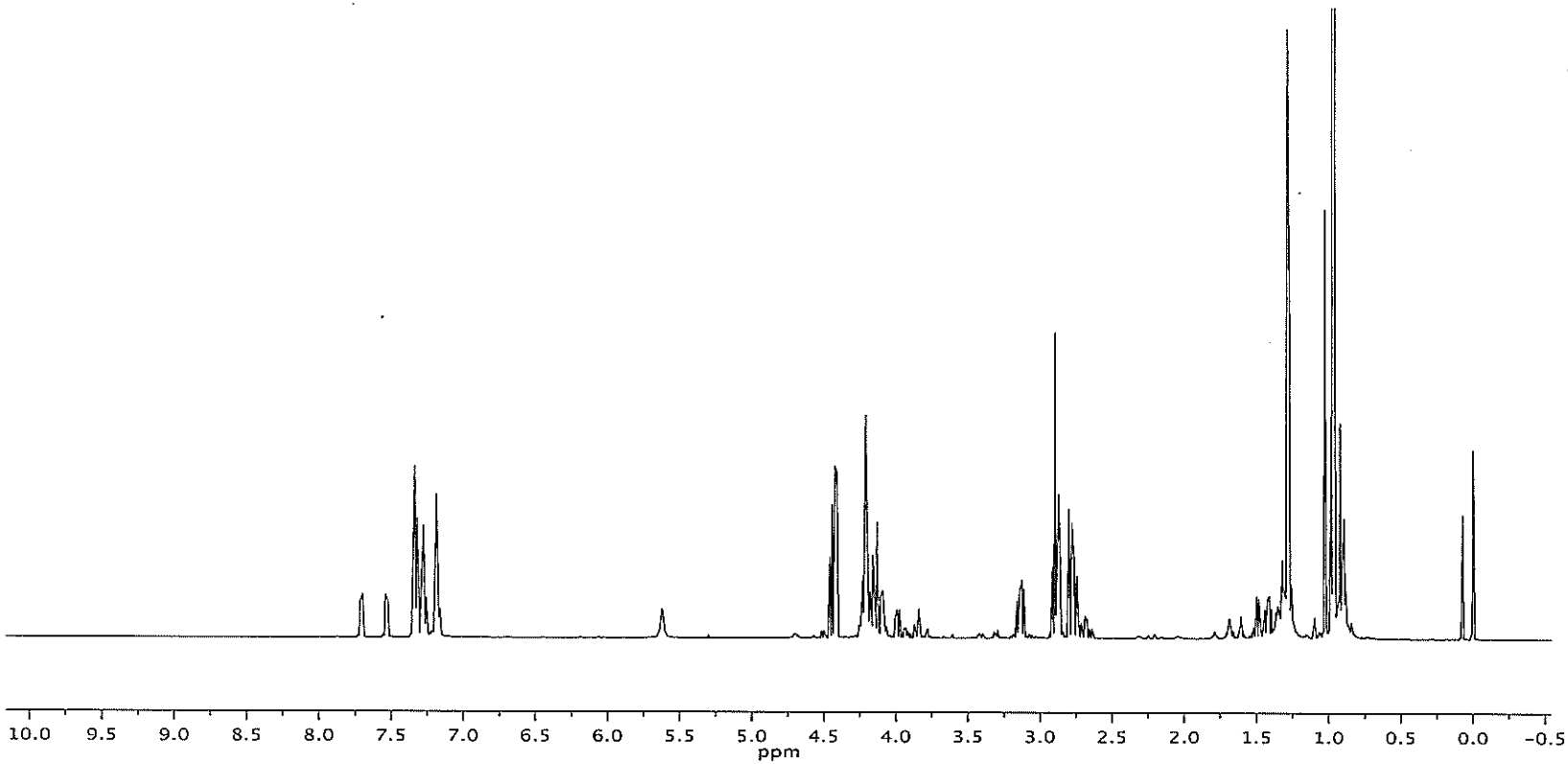

174.2
170.8
160.1
129.8
127.1
114.3
82.4
61.9
55.4
48.8
32.6
14.1
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
ppm

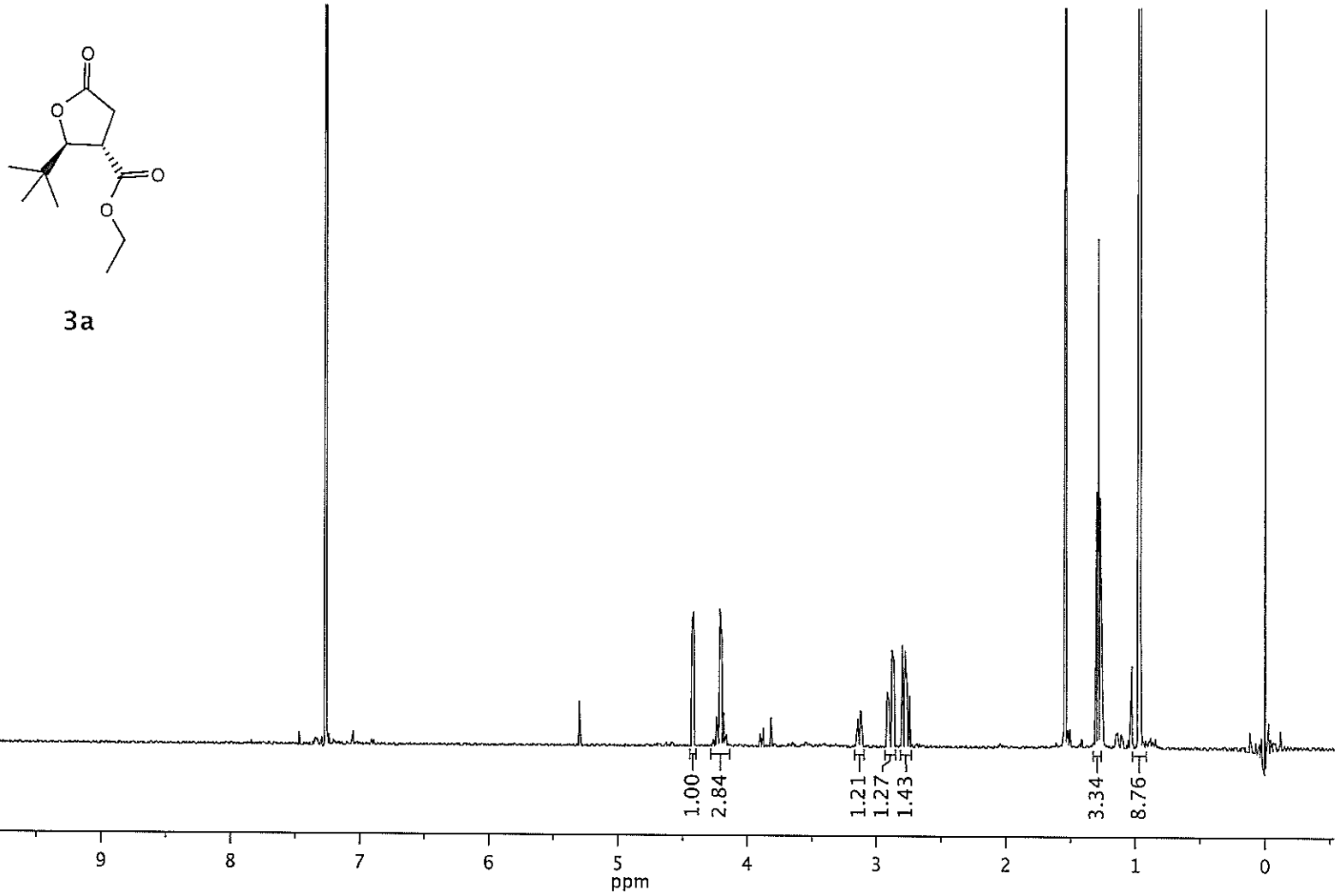
2a

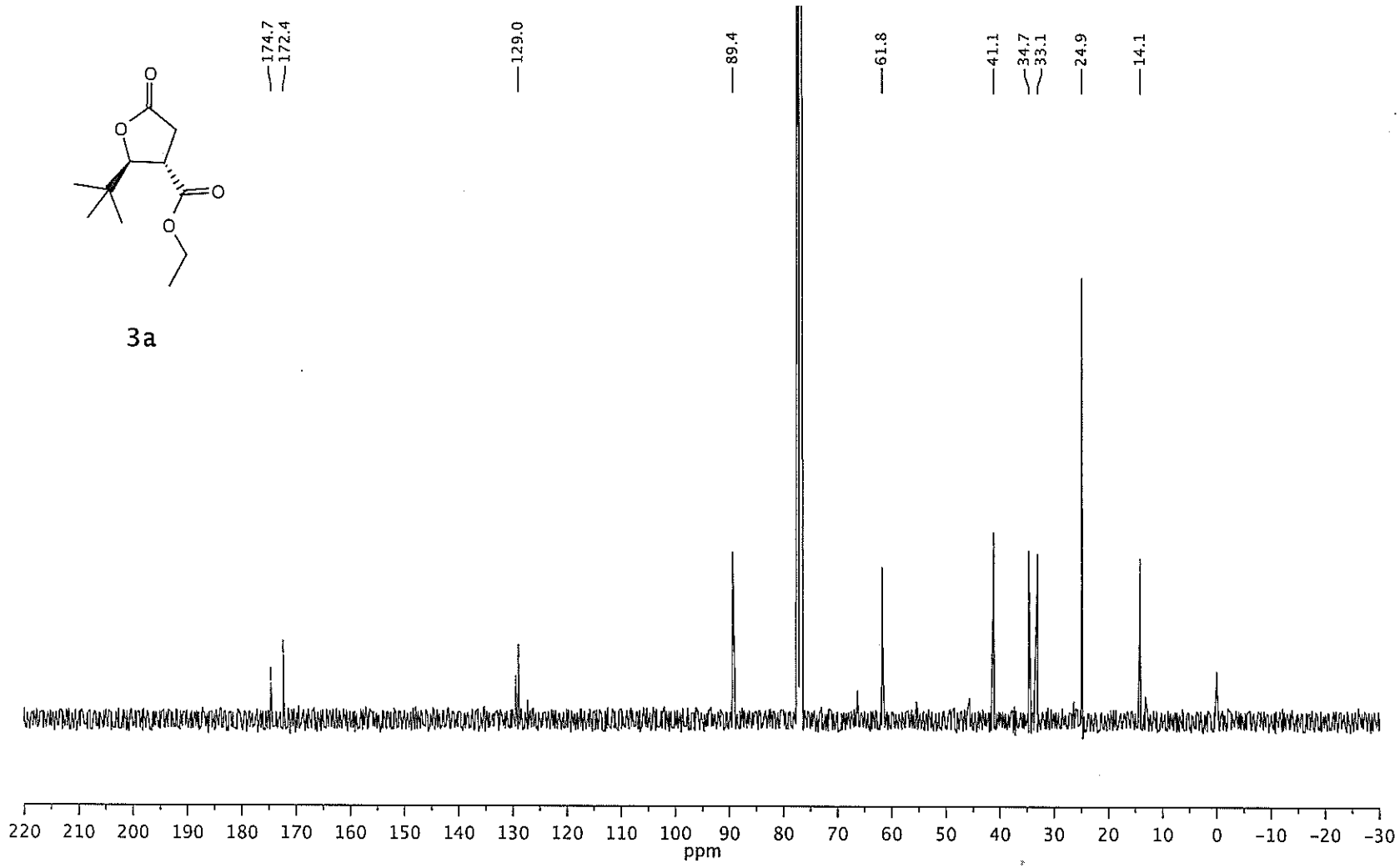

2b
1.52
1.66
1.01
5.66
1.10
1.15
2.60
10
9
8
7
6
5
4
3
2
1
0
ppm

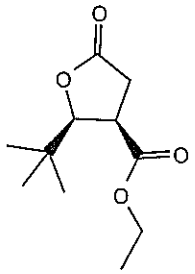

a. Et_2Zn / CH_2I_2
b. $(CH_3)_3$-C-CHO
c. rt, 12 h
Bn
OEt
CO_2Et
CO_2Et

54 **3a** **3b**

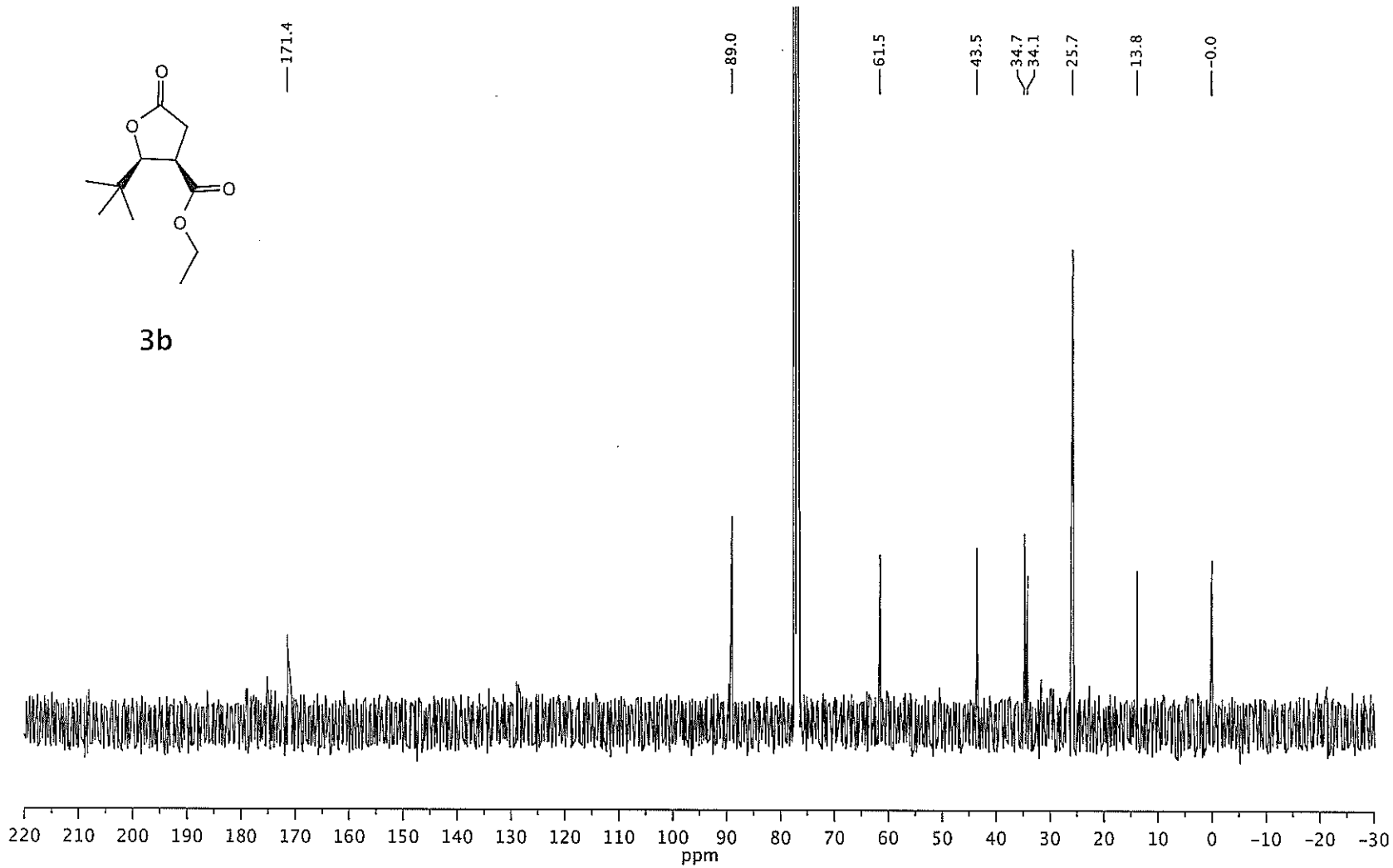

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

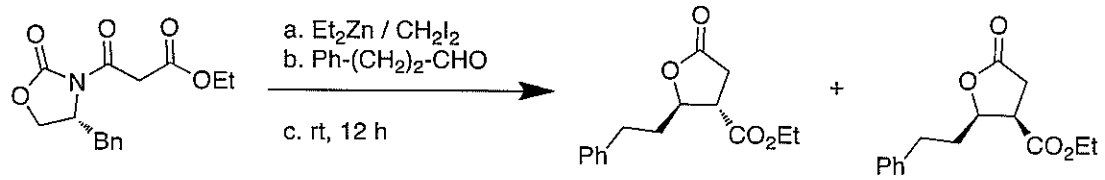

3a
1.00
2.84
1.21
1.27
1.43
3.34
8.76
10
9
8
7
6
5
4
3
2
1
0
ppm


174.7
172.4
129.0
89.4
61.8
41.1
34.7
33.1
24.9
14.1
O
O
O
O
3a
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
ppm

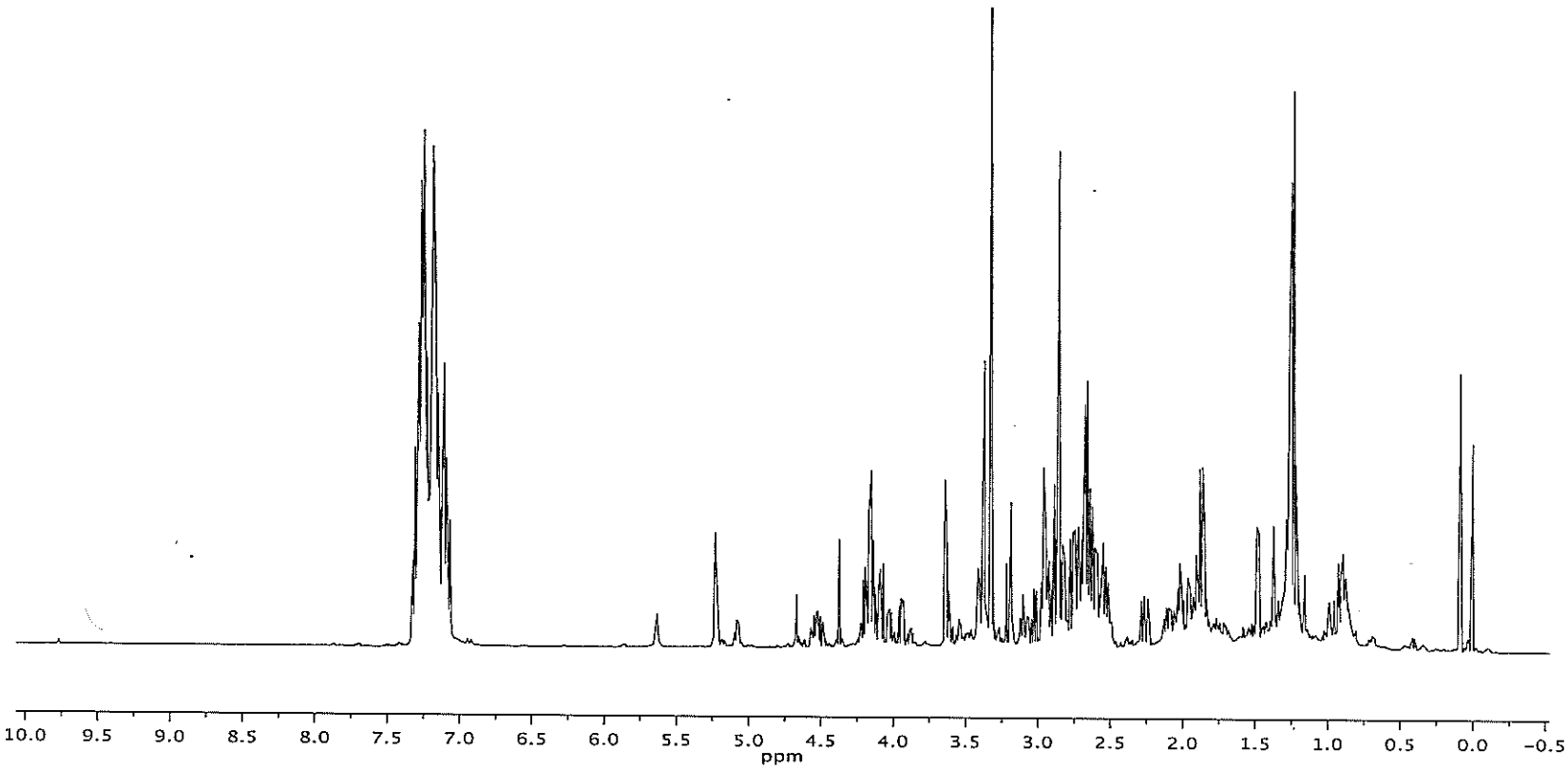


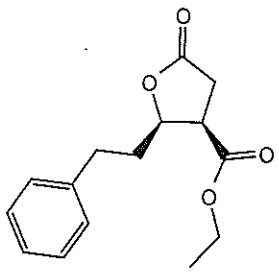
3b


171.4
89.0
61.5
43.5
34.7
34.1
25.7
13.8
-0.0
3b
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
ppm

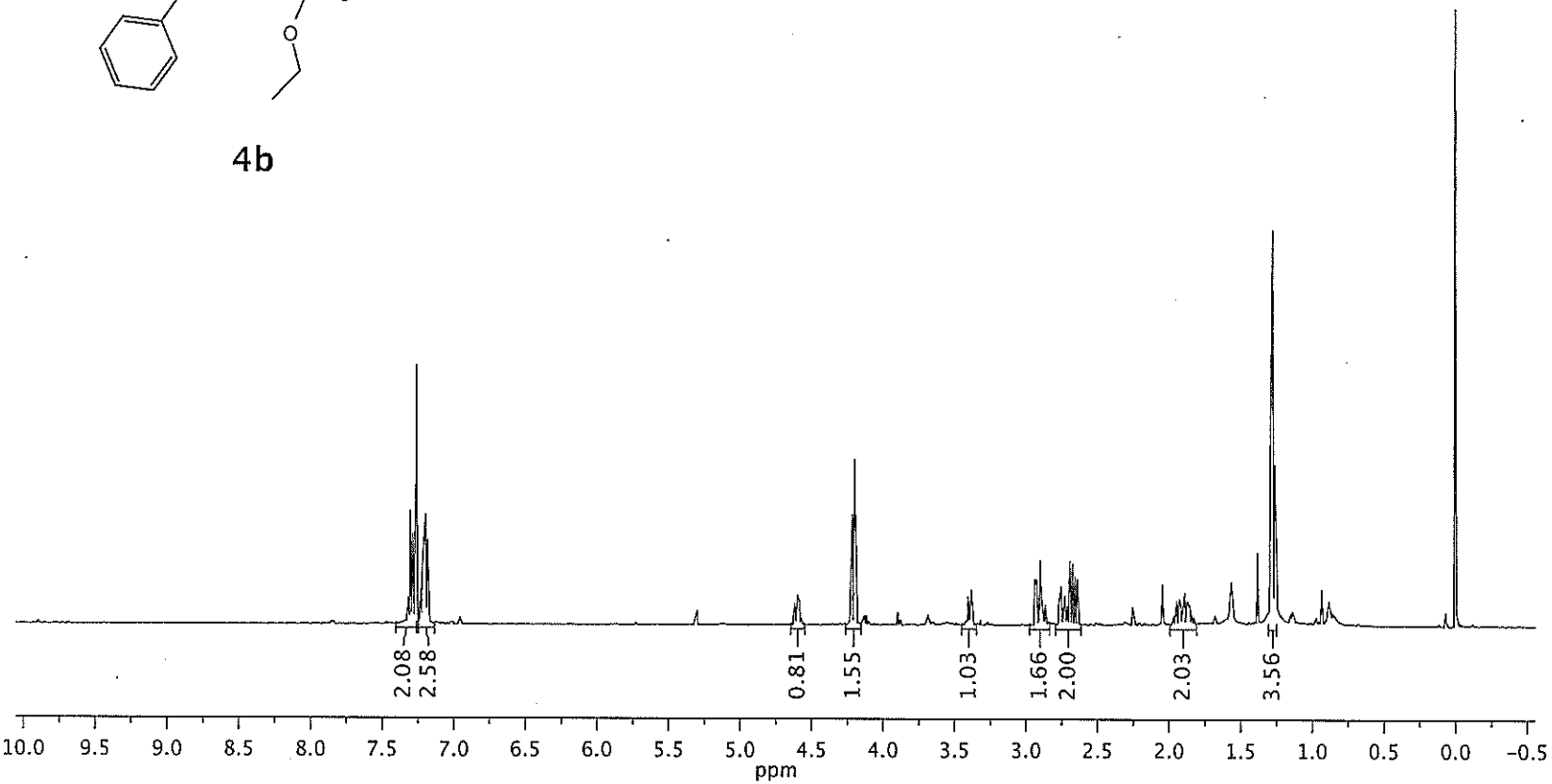

a. Et_2Zn / CH_2I_2
b. Ph-$(CH_2)_2$-CHO
c. rt, 12 h
OEt
Bn
CO_2Et
Ph
+

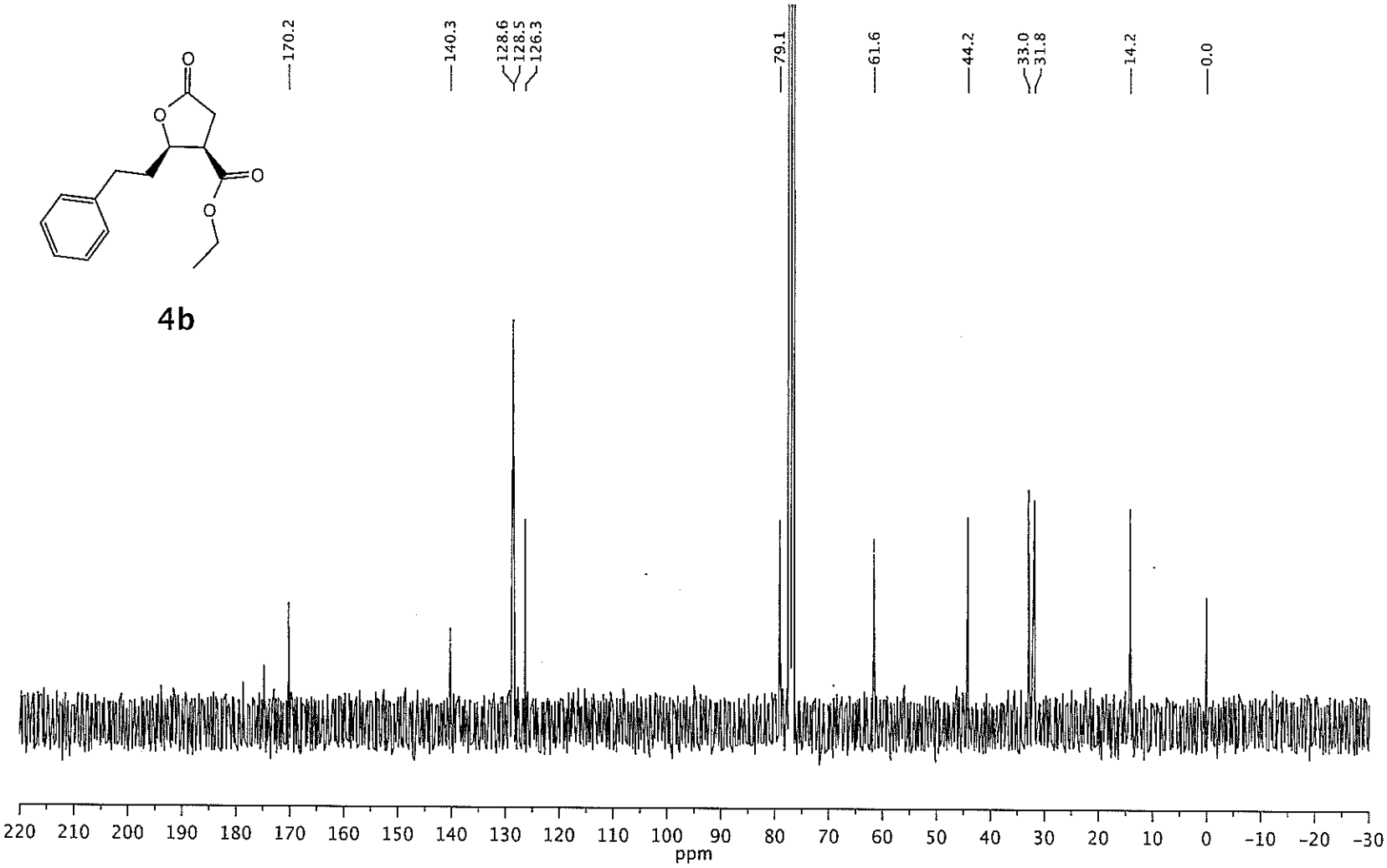
54 **4a** **4b**

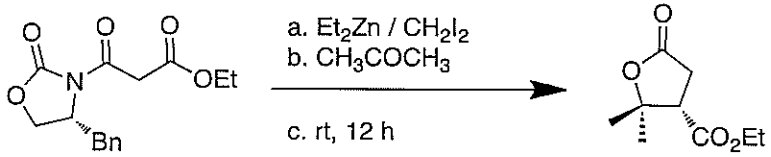

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm



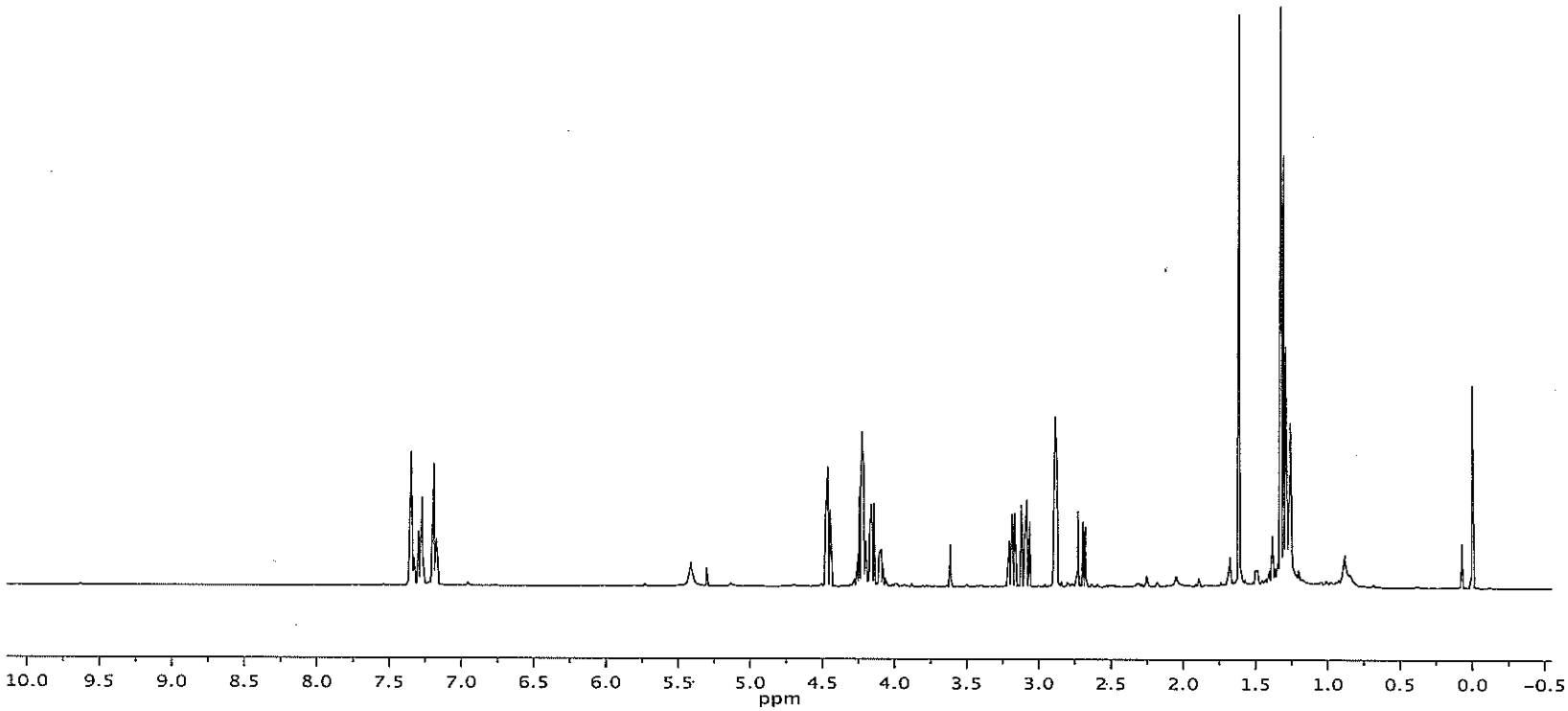
4b

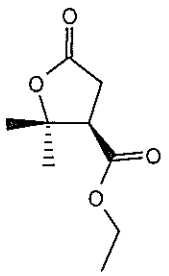

2.08
2.58
0.81
1.55
1.03
1.66
2.00
2.03
3.56
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm


170.2
140.3
128.6
128.5
126.3
79.1
61.6
44.2
33.0
31.8
14.2
0.0
4b
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
ppm


a. Et_2Zn / CH_2I_2
b. CH_3COCH_3
c. rt, 12 h
OEt
Bn
CO_2Et

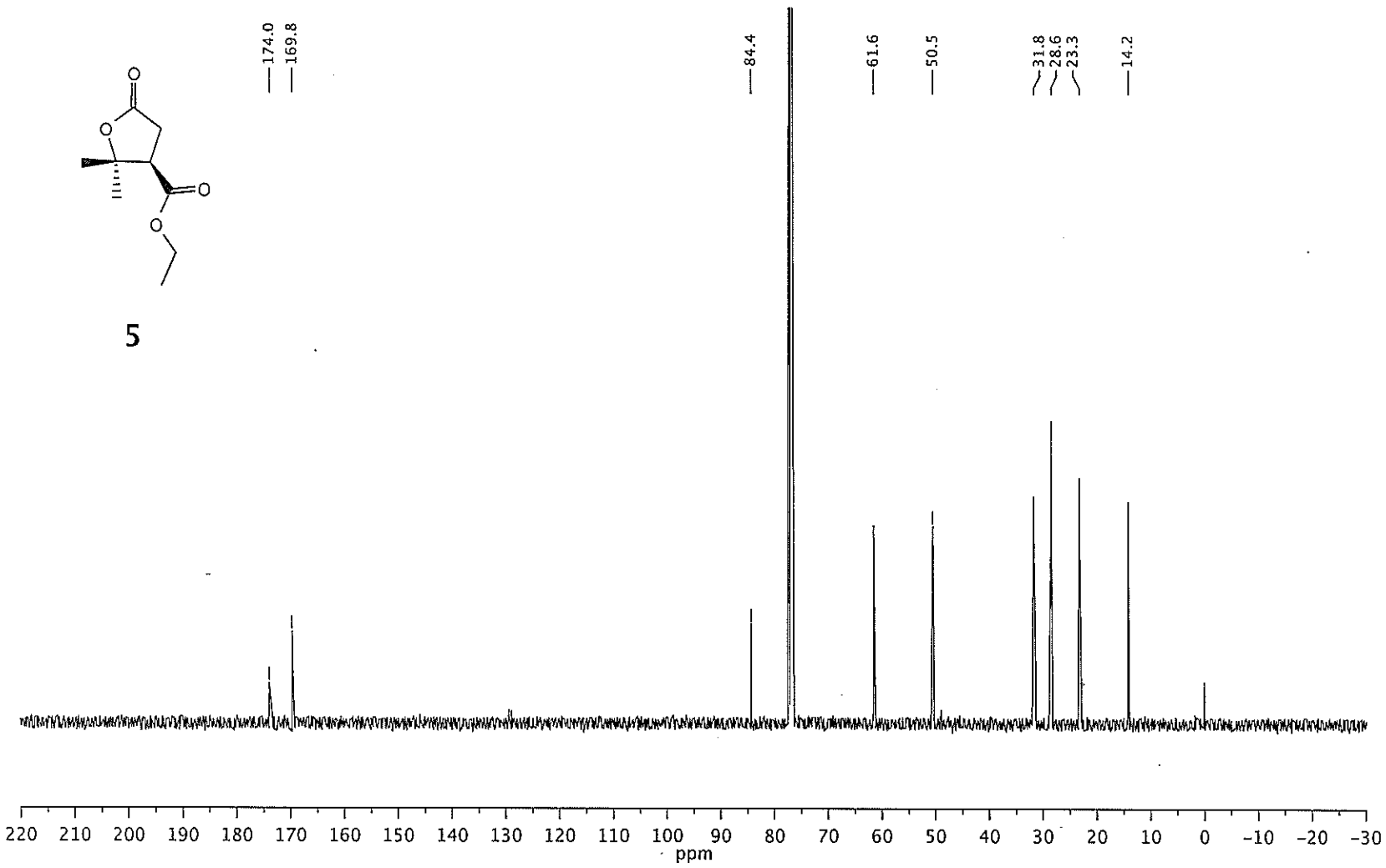
54 **5**


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

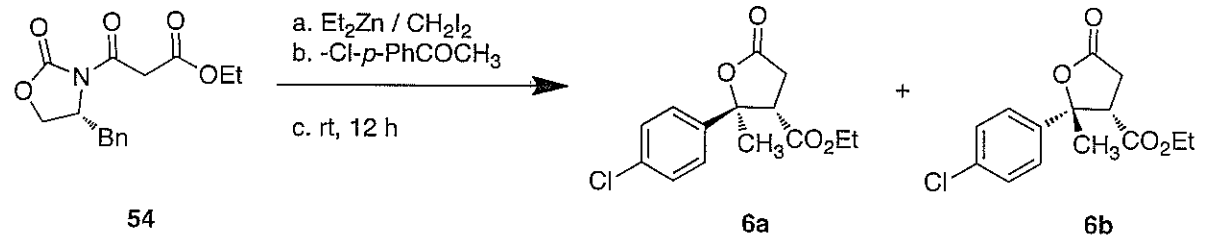


5

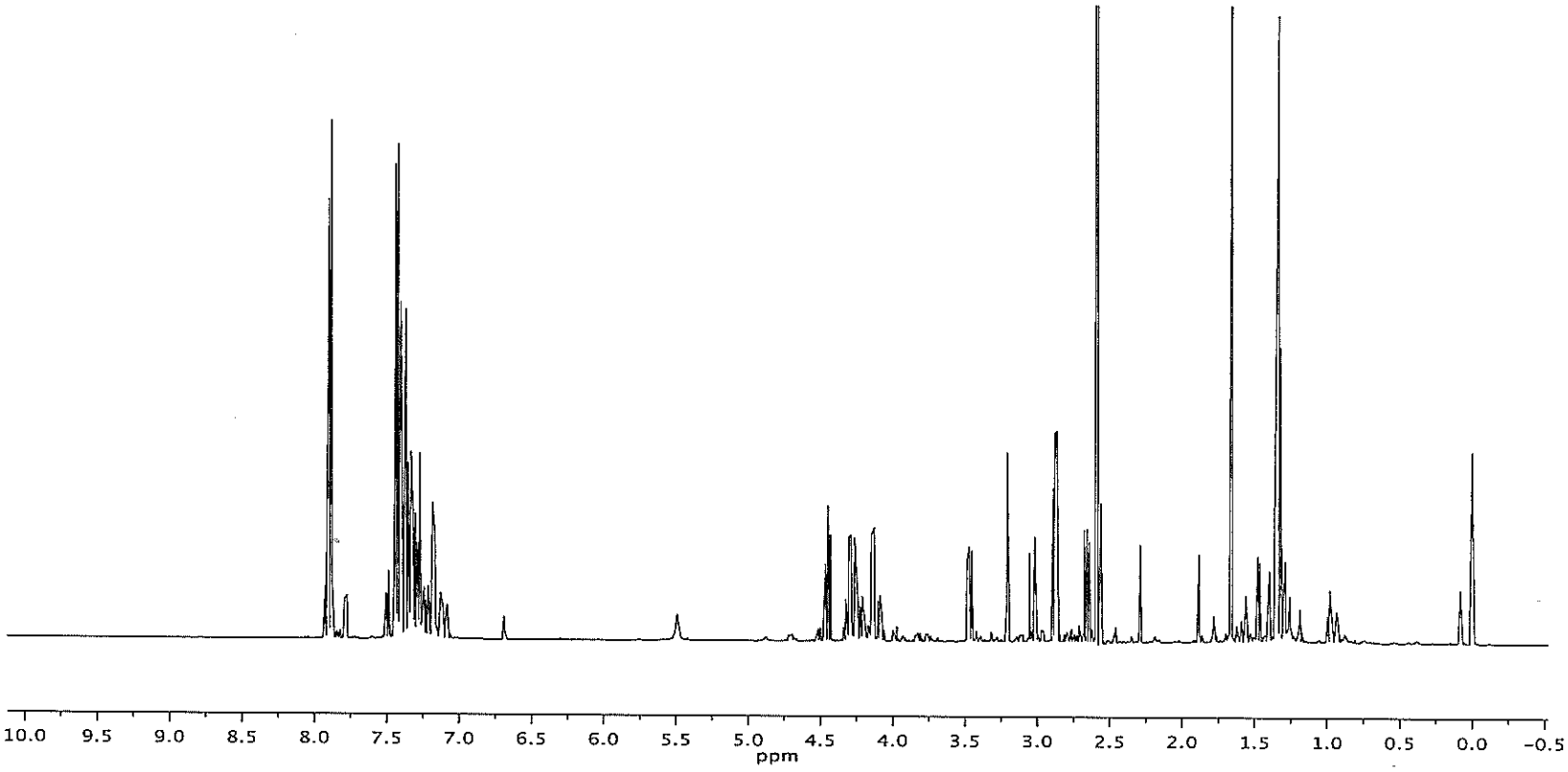
2.30
0.98
1.03
1.08
3.00
6.24
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

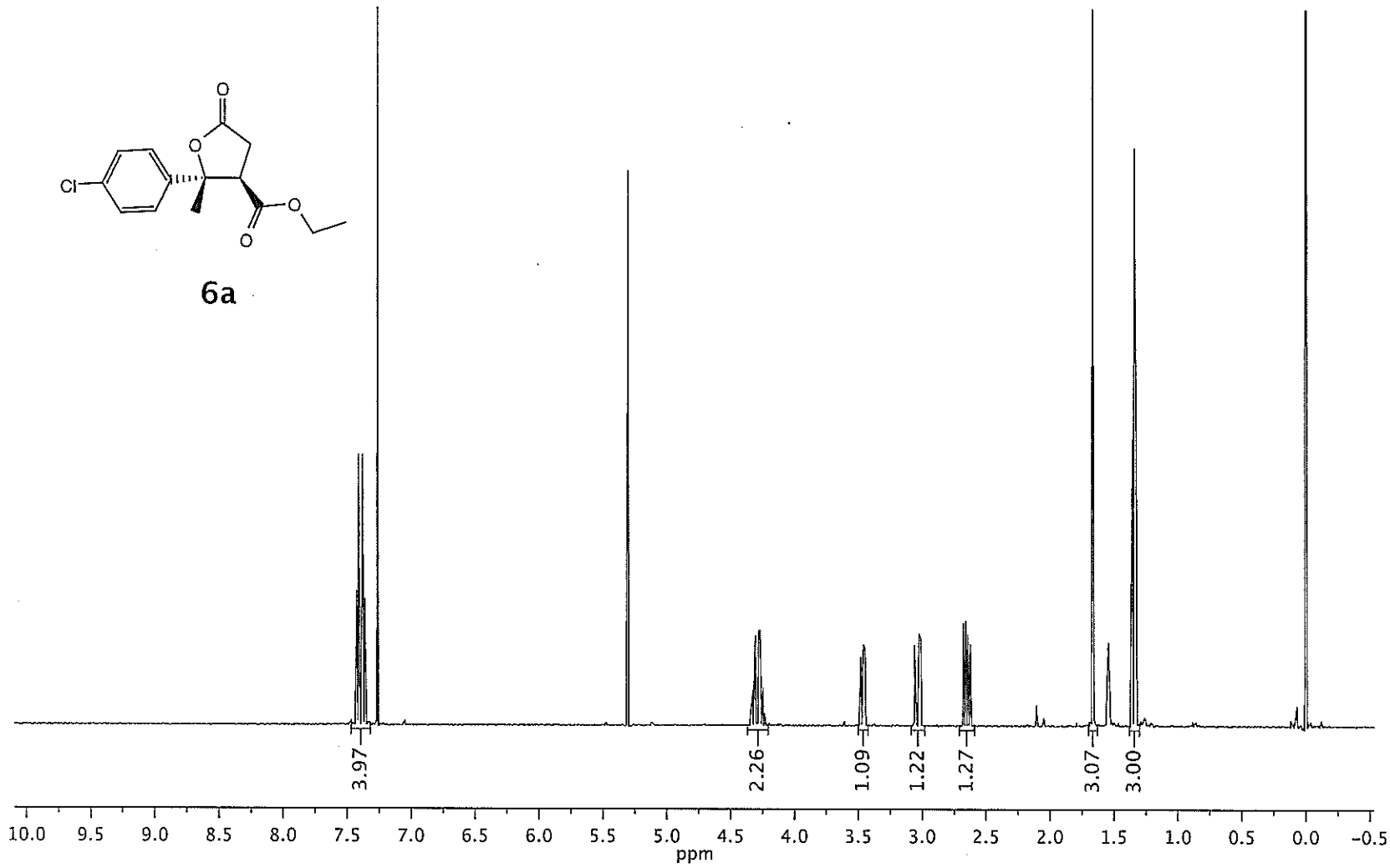

174.0
169.8
84.4
61.6
50.5
31.8
28.6
23.3
14.2
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
ppm

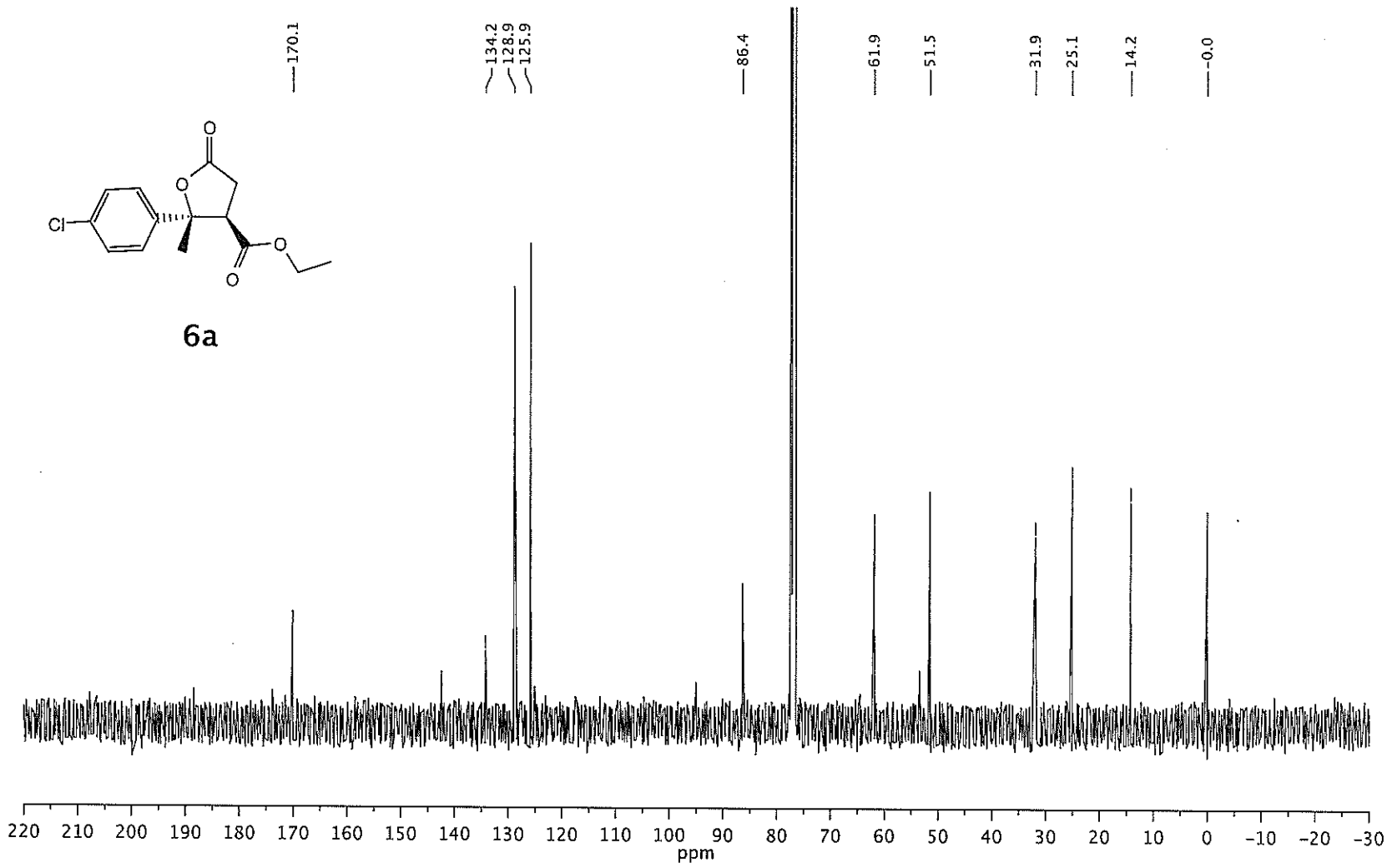
5

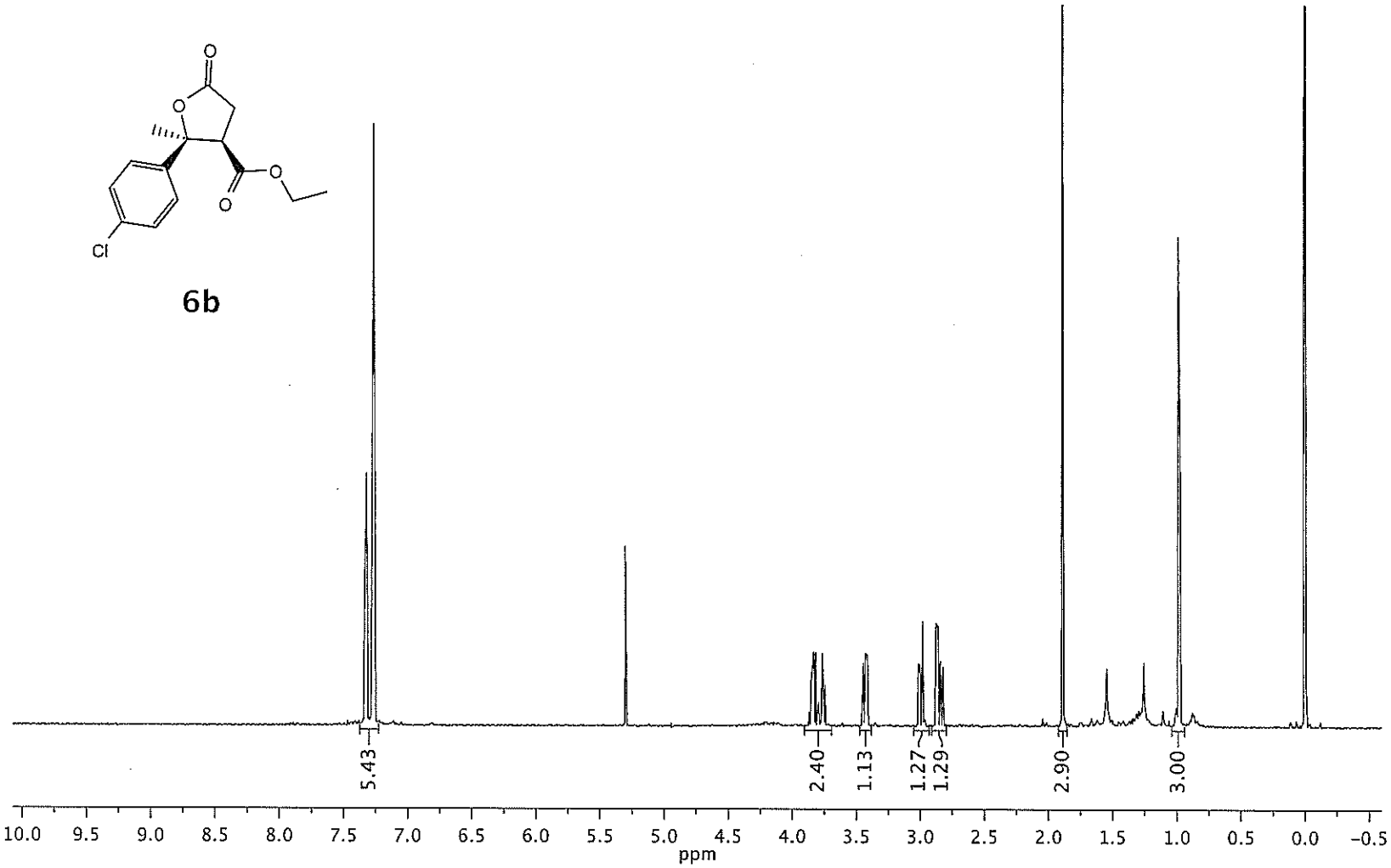

a. Et_2Zn / CH_2I_2
b. -Cl-*p*-$PhCOCH_3$
c. rt, 12 h
OEt
Bn
Cl
CH_3CO_2Et
+

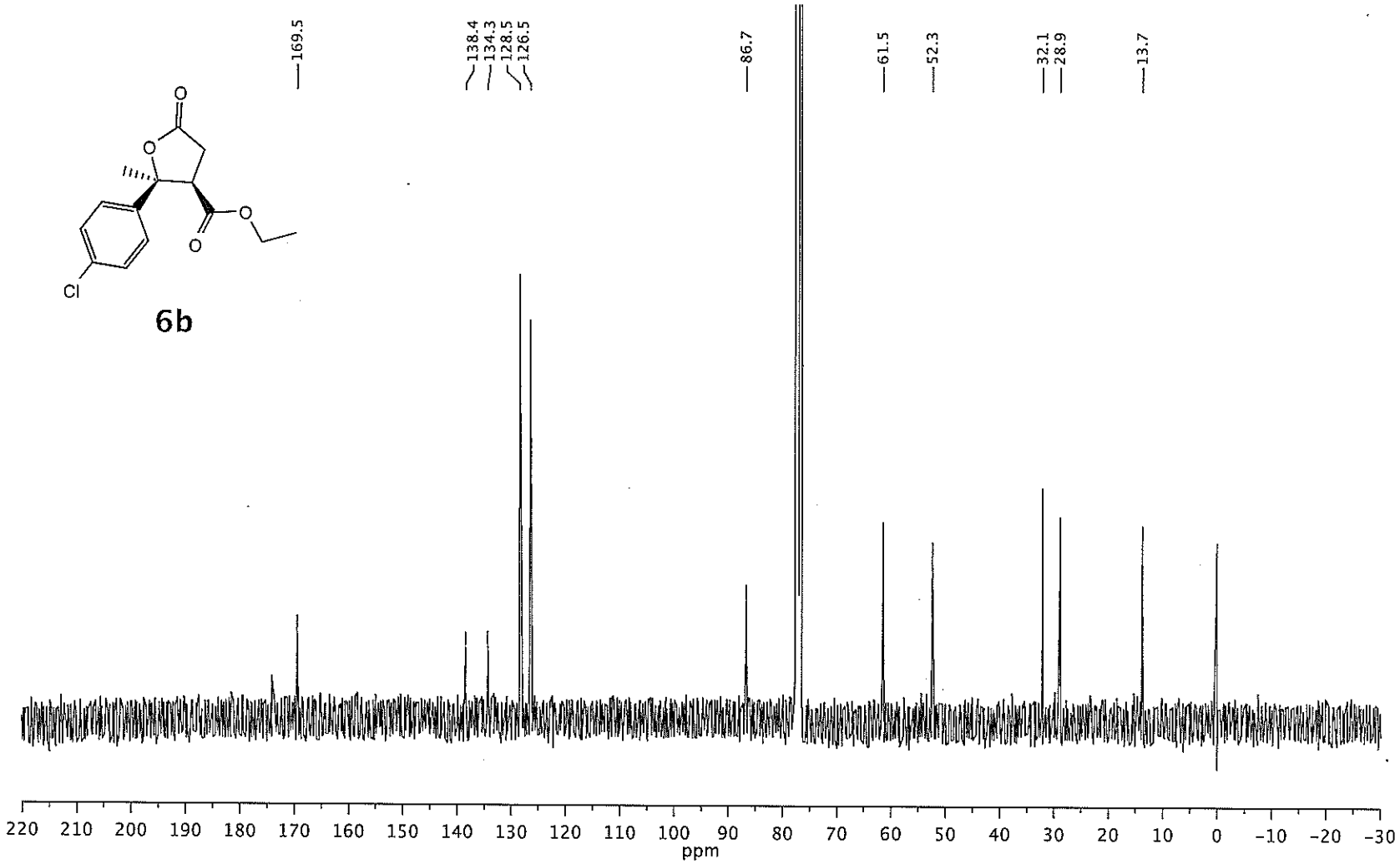
54 6a 6b

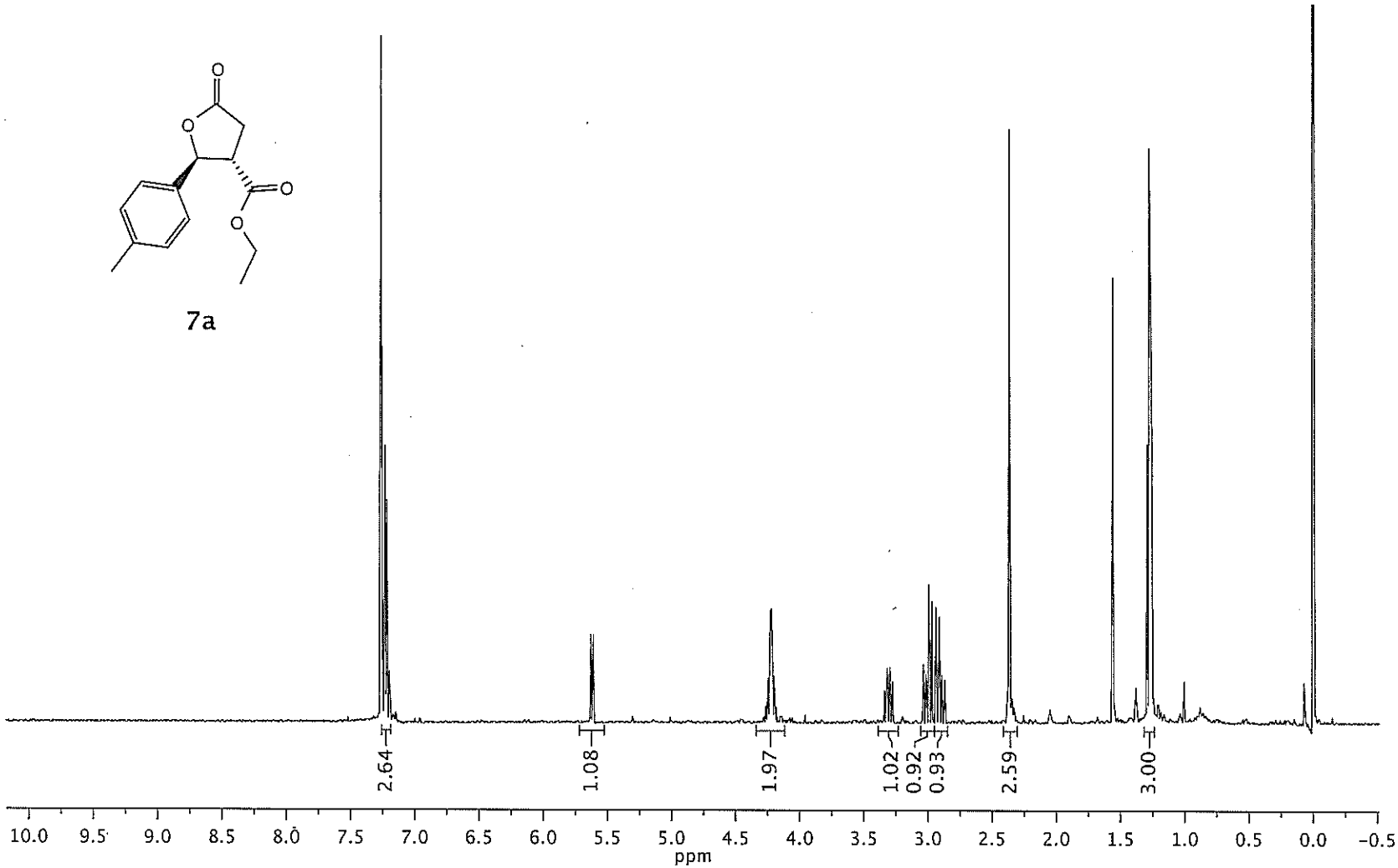

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

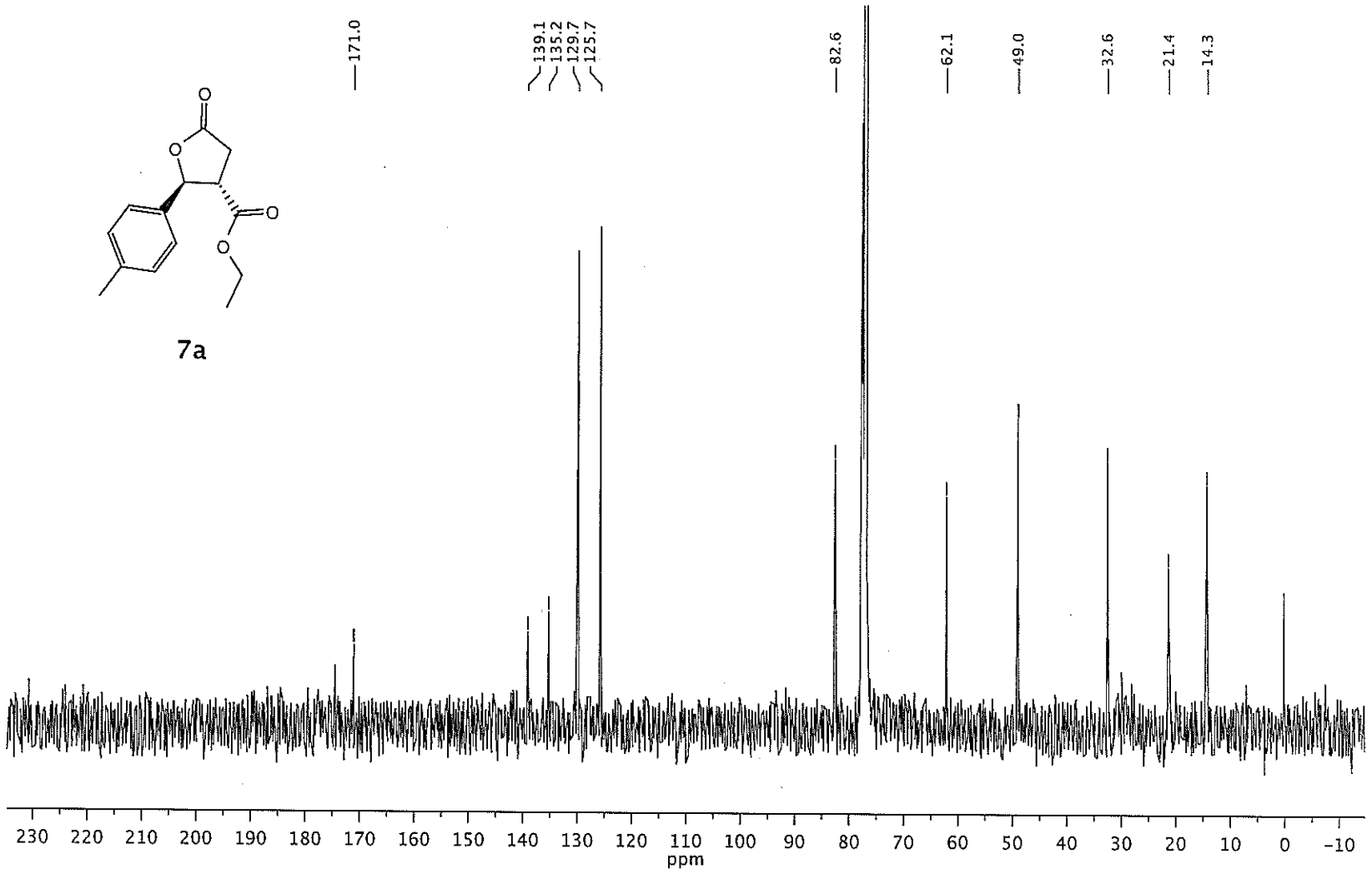

Cl
O
O
O
O
O
6a
3.97
2.26
1.09
1.22
1.27
3.07
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

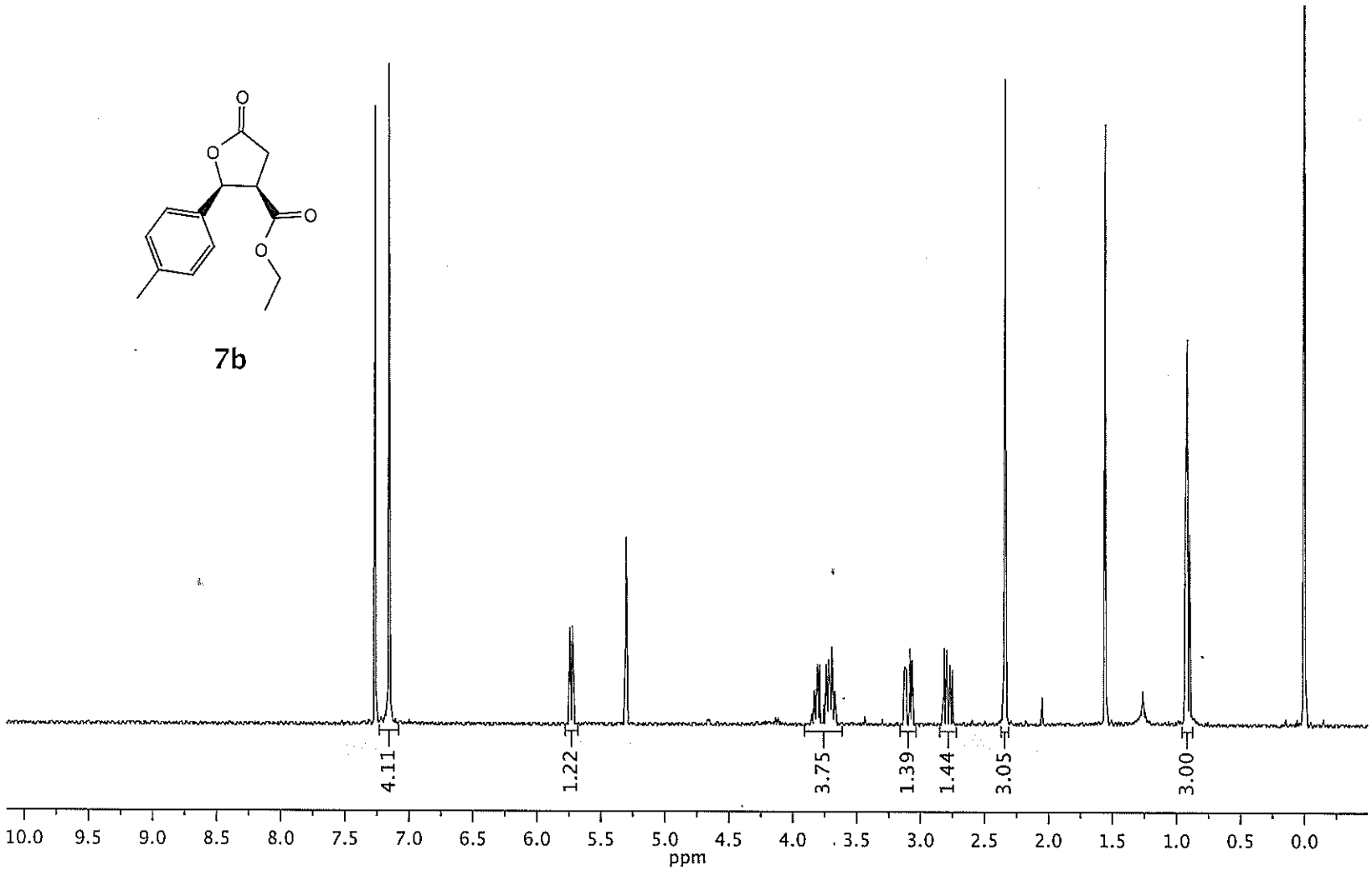

170.1
134.2
128.9
125.9
86.4
61.9
51.5
31.9
25.1
14.2
0.0
Cl
O
O
O
O
6a
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
ppm

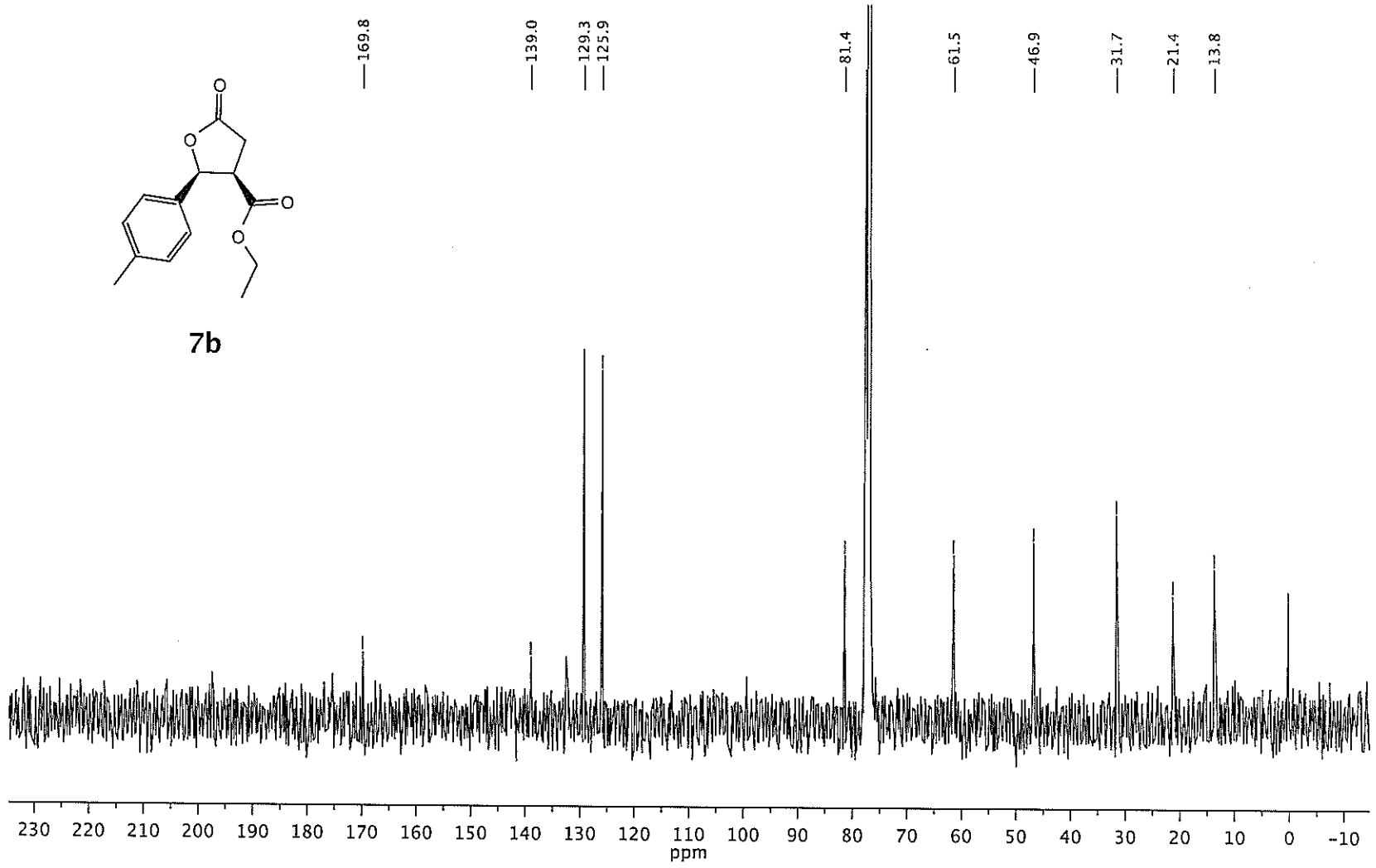

O
O
O
O
Cl
6b
5.43
2.40
1.13
1.27
1.29
2.90
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

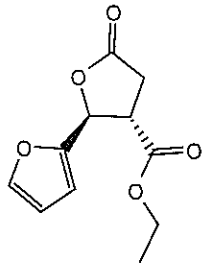

169.5
138.4
134.3
128.5
126.5
86.7
61.5
52.3
32.1
28.9
13.7
O
O
O
O
Cl
6b
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
ppm


7a
2.64
1.08
1.97
1.02
0.92
0.93
2.59
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm


171.0
139.1
135.2
129.7
125.7
82.6
62.1
49.0
32.6
21.4
14.3
7a
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

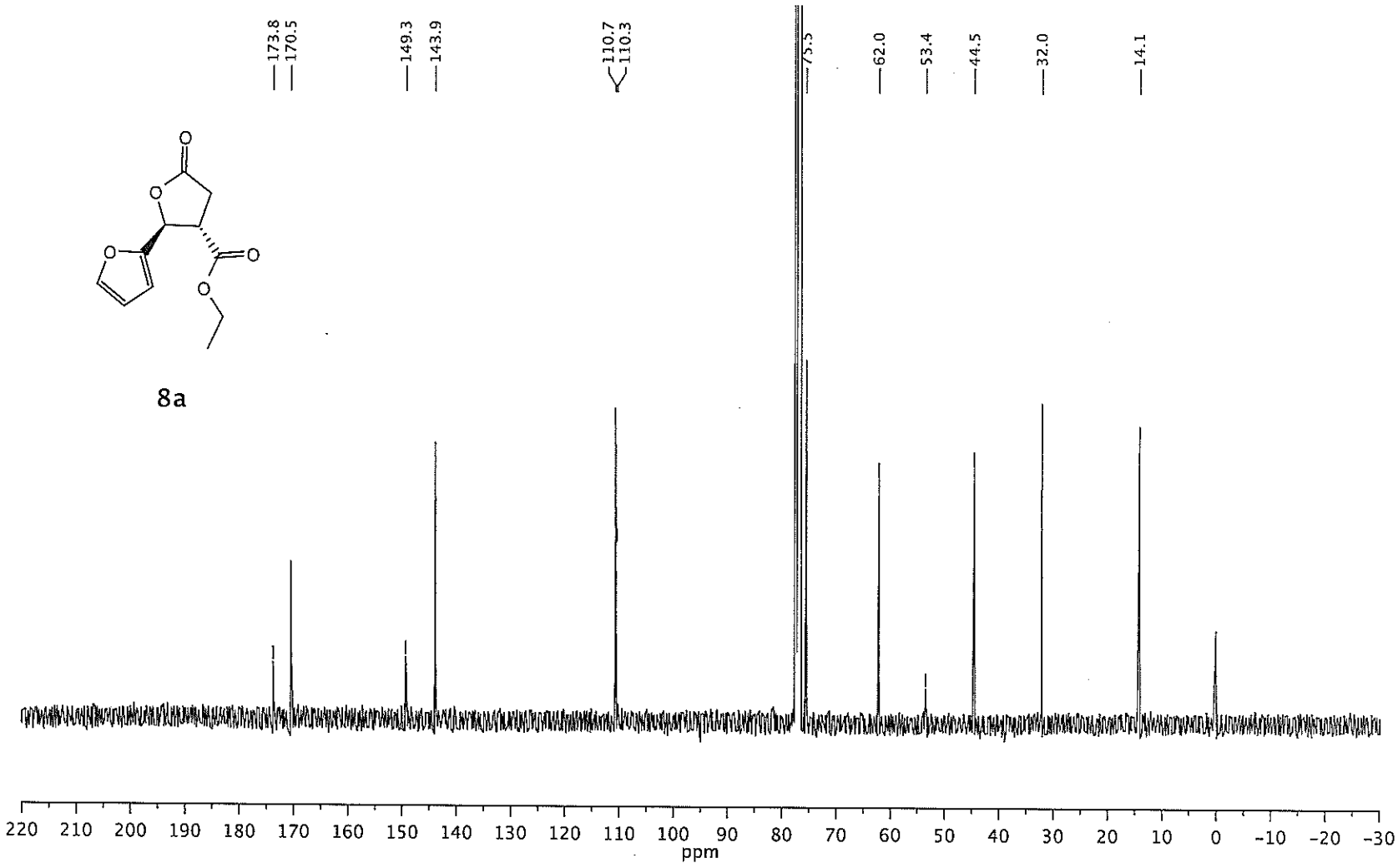

7b
4.11
1.22
3.75
1.39
1.44
3.05
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


169.8
139.0
129.3
125.9
81.4
61.5
46.9
31.7
21.4
13.8
7b
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



8a

0.86
0.89
0.87
0.96
1.95
0.98
2.08
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm


173.8
170.5
149.3
143.9
110.7
110.3
75.5
62.0
53.4
44.5
32.0
14.1
8a
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
ppm